CARBON TETRACHLORIDE

INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive and susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation, or certain non-symptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

EXECUTIVE SUMMARY

Carbon tetrachloride (CAS No. 56-23-5) is a colorless, nonflammable, heavy liquid only slightly soluble in water that is used as a laboratory and industrial solvent, an intermediate in the synthesis of trichlorofluoromethane and dichlorodifluoromethane, and was formerly used as a dry-cleaning agent, grain fumigant, anthelmintic (destructive to worms, especially parasitic varieties), and fire suppressant.

Numerous case reports were available regarding acute inhalation exposure of humans to carbon tetrachloride although most lacked definitive exposure terms. These reports, however, affirmed the hepatotoxic and renal toxicity of carbon tetrachloride as well as a delayed response for serious and fatal effects. Additionally, data from controlled exposures of humans to carbon tetrachloride were also available.

Animal toxicity data for inhaled carbon tetrachloride indicate hepatotoxic and renal effects, as well as anesthetic-like effects, as primary endpoints. The most sensitive endpoint for evaluating the toxicity of carbon tetrachloride in animals appears to be measurement of serum enzyme activities that reflect hepatic damage. Several studies provided lethality data for various concentrations and exposure durations but data regarding nonlethal effects were limited or available only from long-term exposure studies.

Studies in animals have shown the metabolism and disposition of carbon tetrachloride to be complex and varied among species. Although the precise mechanism of toxicity is equivocal, the biotransformation of carbon tetrachloride by the monooxygenase enzymes (specifically CYP2E1) to reactive intermediates is critical for expression of toxicity. It is this activation process that is critical in modifying the toxic response to carbon tetrachloride.

The AEGL-1 values were based upon a controlled exposure of human volunteer subjects to 76 ppm for four hours (Davis, 1934). No central nervous system (CNS) effects or renal effects were associated with this exposure. Development of AEGL values for the various exposure periods was based upon the exponential function, $C^n \times t = k$ (ten Berge et al., 1986), where n = 2.5 as determined by the lethal response of rats to various exposures of carbon tetrachloride. The AEGL-1 values were adjusted by an uncertainty factor of 10 to account for the protection of sensitive individuals (such as users of alcohol) who, due to metabolism and disposition factors, are known to be more susceptible to the toxic effects of carbon tetrachloride.

The AEGL-2 was also based upon human data from controlled exposure experiments in which subjects experienced CNS effects characterized by headache, nausea and vomiting following 9-minute exposure to 1191 ppm carbon tetrachloride (Davis, 1934). It is believed that these effects may impair escape. The AEGL-2 values were derived with temporal scaling based upon the exponential function where n = 2.5. The AEGL values were further adjusted by the application of an uncertainty factor of 3 ~~10~~ to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride. Because the CNS effects are independent of metabolism (a critical factor in lethal responses), the uncertainty factor was limited to 3.

The AEGL-3 was based upon an estimated lethality threshold (1-hr LC_{01} of 5,135.5 ppm) using data from multiple studies on laboratory rats (Adams et al.,1952; Dow Chemical, 1986). Temporal scaling using the exponential function where n = 2.5 was derived from lethality data and used to develop values for AEGL-specific exposure durations. An uncertainty factor of 10 was again applied to account for individuals who may be more susceptible to the toxic effects of carbon tetrachloride (e.g., P-450 induction by ethanol consumption and overall variability in metabolism and disposition of the chemical). Results of

physiologically-based pharmacokinetic (PBPK) modeling have clearly indicated rodents as notably more susceptible to carbon tetrachloride toxicity than are humans. Therefore, the interspecies uncertainty factor was limited to 1. Additional adjustment of the AEGL-3 values did not appear to be warranted because animal data showed that long-term exposures to carbon tetrachloride above the AEGL-3 values did not result in notable toxic effects.

Although a carcinogenic response following oral exposure of laboratory species has been demonstrated, quantitative data for inhalation exposures were unavailable. However, a unit risk of 1.5E-5 per $\mu g/m^3$ has been established based upon route-to-route extrapolation from carcinogenicity data for oral exposures in various laboratory species. An estimation of AEGLs based upon carcinogenic potential was conducted but the assessment revealed that AEGLs derived from noncarcinogenic toxicity endpoints were more applicable for human health protection relative to adverse effects following acute inhalation exposure.

Carbon tetrachloride **NAC/Interim: 01/2008**

The AEGL values for carbon tetrachloride are listed in the table below.

AEGL VALUES FOR CARBON TETRACHLORIDE (ppm [mg/m^3])

Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	58 [365]	58 [365]	44 [277]	25 [157]	19 [120]	Absence of CNS or renal effects in human volunteer subjects exposed to 76 ppm for 4 hrs (Davis, 1934)
AEGL-2	380 [2390]	250 [1573]	190 [1195]	100 [629]	81 [509]	Nausea, vomiting, headache in human subjects exposed to 1191 ppm for 9 minutes (Davis, 1934)
AEGL-3	1100 [6920]	680 [4227]	520 [3270]	300 [1887]	220 [1384]	Lethality in rats; estimated LC_{01} (Adams et al., 1952; Dow Chemical, 1986)

References

Adams, E.M., Spencer, H.C., Rowe, V.K., McCollister, D.D., Irish, D.D. 1952. Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Arch. Ind. Hyg. Occup. Med. 6: 50-66.

Davis, P. A. 1934. Carbon tetrachloride as an industrial hazard. JAMA. 103: 962-966.

Dow Chemical. 1986. Comparison of the result of exposure of rats and cavies to the vapors of carbon tetrachloride and bromochloromethane. Dated 7/11/60. EPA-OTS 86-870002363.

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1. INTRODUCTION

Carbon tetrachloride is a colorless, nonflammable, heavy liquid (Budavari et al., 1989). It has been used as a laboratory and industrial solvent, as an intermediate in the synthesis of trichlorofluoromethane and dichlorodifluoromethane, and was formerly used as a dry-cleaning agent, grain fumigant, anthelmintic, and as a fire suppressant (Royal Soc. Chem., 1989). Carbon tetrachloride has a sweet, pungent odor that is not unpleasant. An odor threshold of 21.4-238.5 ppm has been reported (Billings and Jones, 1981; Ruth, 1989).

The hepatotoxicity of carbon tetrachloride is well documented and has been reviewed by Rechnagel and Glende (1973). Carbon tetrachloride is also known to affect the central nervous system and to induce renal toxicity. The toxicity of carbon tetrachloride has been recently summarized (ATSDR, 2003 1993). It's volume of production and use, and its persistence in the environment maintain a high-interest profile for carbon tetrachloride.

For derivation of AEGL values, acute exposure studies are preferentially examined. Subchronic and chronic studies generally have not been included in the data analysis for AEGL derivation because of the great uncertainty in extrapolating such data to acute exposure scenarios. Such studies may be addressed when the data provided relate to effects following acute exposures, meaningful insight into understanding toxicity mechanisms, or for other special considerations. The primary physicochemical data for carbon tetrachloride are presented in Table 1.

TABLE 1. PHYSICOCHEMICAL DATA FOR CARBON TETRACHLORIDE

Synonyms	carbon chloride; carbona; carbon tet; freon 10; methane tetrachloride; perchloromethane; tetrachloromethane; tetrachlorocarbon; tetrafinol	Royal Soc. Chemistry, 1989
CAS Registry No.	56-23-5	Budavari et al., 1989
Chemical formula	CCl_4	Budavari et al., 1989
Molecular weight	153.84	Budavari et al., 1989
Physical state	liquid	Budavari et al., 1989
Vapor pressure	15.2 kPa @ 25°C	Lide and Frederikse, 1993
Density	1.589 at 25°C	Budavari et al., 1989
Boiling/freezing point	77°C/-23°C	Lide and Frederikse, 1993
Solubility	1 mL/2,000 mL water; miscible with alcohol, benzene, chloroform, ether, petroleum ether, oils, carbon disulfide	Budavari et al., 1989
Conversion factors in air	1 mg/m^3 = 0.159 ppm 1 ppm = 6.29 mg/m^3	

2. HUMAN TOXICITY DATA

2.1 Acute Lethality

The acute toxicity and lethality of carbon tetrachloride in humans following inhalation exposure has been reviewed by Norwood et al. (1950), Umiker and Pearce (1953), and ATSDR (2003). Most human case reports lack definitive quantitative exposure data. The more relevant reports are summarized in the following sections. Most lethal cases involve renal failure and are characterized by oliguria or anuria prior to death.

Norwood et al (1950) reported on 58 cases (55 of which were industrial exposures) involving exposure to carbon tetrachloride vapors. Of the three non-industrial exposures, two resulted in fatalities, and one resulted in serious health effects requiring hospitalization. For one of the fatalities, an exposure reconstruction provided a measured exposure concentration of 250 ppm (analytical techniques not provided). Using the size of the room (15 ft x 16 ft x 8 ft), the room ventilation rate (144 cu. ft/min), the exposure duration (15 minutes), and the volume of carbon tetrachloride used (2.5 liters), the reconstruction duplicated to the extent possible the conditions under which the incident occurred. For this case, the subject was a 22-year old male who was a heavy consumer of alcohol for many years. The exposure involved the subject cleaning a floor with carbon tetrachloride. Following a fifteen minute exposure, the subject experienced headache and dizziness. The subject then experienced generalized aches and pains, and episodic nausea and vomiting of 6-hour duration whereupon he was admitted to the hospital. Although physical and laboratory findings were unremarkable for several days, by the fifth day there was evidence of renal involvement which progressed to renal insufficiency and death by day six. Two individuals continued the floor cleaning and were subjected to the same exposure conditions for approximately four hours. These two individuals reported very mild headaches and some dizziness which subsided after the work was completed. It is uncertain if dermal contact was an issue in this accidental exposure, although the subject's alcohol consumption and potentiated carbon tetrachloride metabolism was likely an important contributing factor in the final outcome.

Another fatality was also reported by Norwood et al. (1950) that involved an intoxicated woman with a respiratory infection using carbon tetrachloride to clean her trailer. The subject experienced nausea and vomiting, abdominal tenderness, and anuria, and died twelve hours after admission to the hospital. No exposure terms were presented regarding this case report.

2.2 Nonlethal Toxicity

2.2.1 Acute Exposure Case Reports

Although many case reports are available regarding acute exposures to carbon tetrachloride, most are deficient in definitive exposures terms. Most of the reports do, however, describe a similar clinical picture of carbon tetrachloride poisoning that includes initial dizziness and nausea, abdominal discomfort, oliguria and/or anuria with subsequent renal failure and death (Ashe and Sailer, 1942; Gray, 1947; Jennings, 1955; Guild et al., 1958; New et al., 1962; Ruprah et al., 1985; Manno et al., 1996). The increased potential for carbon tetrachloride-induced toxicity (both renal and hepatic) associated with alcohol consumption and/or abuse has been documented in several of the available case reports.

Davis (1934) reported the results of several experiments in which human subjects were exposed to carbon tetrachloride. The carbon tetrachloride concentrations were determined based on the room volume and the amount of carbon tetrachloride necessary to achieve the desired concentration; there was no mention of air flow rate or ventilation in the test room. In one experiment four individuals (ages 20, 28, 28, and 30 years; gender not specified) were exposed to 158 ppm carbon tetrachloride for 30 minutes. One subject experienced nervousness and slight nausea but the remaining three were asymptomatic. There were no physiologically significant alterations in blood pressure, heart rate, respiratory rate, blood

counts or hemoglobin content. Urinalyses at 24 hours postexposure revealed no signs of toxicity. In the second experiment, four different subjects (ages 35, 48, 22, and 30; gender not specified) were exposed to a carbon tetrachloride concentration of 76 ppm for two and one-half hours. There were no symptoms or signs of toxicity in any of the subjects. In the third experiment, the same subjects used in the previous experiment were exposed 24 hours later to 76 ppm for four hours without signs or symptoms. Urinalyses at 72 hours postexposure were normal. In the fourth experiment, three additional subjects (ages 20, 45, and 36, gender not specified) were exposed to 317 ppm carbon tetrachloride for 30 minutes. Although clinical tests (blood pressure, hemoglobin, blood count, pulse, and urinalysis) were normal, one subject experienced nausea, another nausea and vomiting, and the third complained of headache. In experiment 5, four subjects (ages 19, 21, 28, and 40; gender not specified) were exposed for 15 minutes to 1,191 ppm carbon tetrachloride. Two of the subjects (one of which could only tolerate a 9-minute exposure) experienced headache, nausea and vomiting, another nausea and vomiting, and another nausea and headache. The pulse rate and blood pressure appeared somewhat elevated, although no base-line data were provided for comparison. Urinalyses at 48 hours postexposure were negative except for slightly increased acidity and phosphates. In experiment six, three subjects (ages, 40, 26, and 19, gender not specified) were exposed to 12,800 ppm for 5, 3, and 7 minutes, respectively. The first subject became dizzy, nauseated, sleepy, and experienced a throbbing headache. The second subject became nervous, nauseated, and listless, and the third subject experienced nausea, vomiting, dizziness, and became sleepy. Clinical examination two weeks postexposure revealed no adverse effects.

In a less controlled experiment, Davis (1934) measured the carbon tetrachloride concentration near the faces of men asked to use the solvent in an enclosed room. Using an alcohol potassium hydroxide and combustion method, the carbon tetrachloride concentration was found to be 0.23 % (≈2,300 ppm). None of the three subjects could work for more than 10 minutes without becoming nauseated and sleepy. One of the three experienced vomiting, dizziness, and a throbbing headache.

Davis et al. (1934) also provided anecdotal data regarding compromised renal function in a worker experimentally exposed to carbon tetrachloride during an 8-hour work day. The concentration was estimated at 0.02% (200 ppm). The renal function recovered only after two months following the exposure.

Smyth et al., (1936) conducted surveys in various occupational settings (e.g., dry cleaning, distillation processes) and found average concentrations of carbon tetrachloride ranging from 10-650 ppm with peak concentrations up to 7,860 ppm. Based upon average working time, 8-hr TWA values of 5-117 ppm were calculated for these subchronic exposure settings. The effects associated with these exposures were minimal (evidence of restricted visual field and elevated bilirubin) but indicative of carbon tetrachloride exposure. Actual daily exposures levels were unknown.

Elkins (1942) summarized the findings of case reports of workers in various facilities including dry cleaning, spot cleaning, multigraphing, and coating. Reports of nausea, vomiting, and weight loss were associated with acute, albeit probably repeated, exposures to carbon tetrachloride concentrations of 20-85 ppm. Elkins proposed that the maximum allowable concentration for carbon tetrachloride should be 25-50 ppm.

Norwood et al (1950) reported on seven non-industrial exposures; two resulted in fatalities (see Section 2.1), and five resulted in serious health effects requiring hospitalization. An exposure reconstruction provided an estimate of the exposure concentration (250 ppm) involved in one of the fatalities which involved a 22-year old male (heavy drinker) who was cleaning the floor. However, two individuals continued the floor cleaning and were subjected to the same exposure conditions for approximately four hours. These two individuals reported very mild headaches and some dizziness which subsided after the work was completed.

Norwood et al. (1950) reported a nonlethal case of carbon tetrachloride poisoning in an individual who was a heavy user of alcohol beverages. Signs and symptoms included nausea, vomiting, weakness, and numbness of extremities or generalized aches and pains. Although the fire extinguisher release took place in a confined area, an exposure concentration was not reported. The exposure duration for this nonlethal case was probably short considering the source of the carbon tetrachloride.

Although lacking in exposure terms, Stevens and Forster (1953) provided case reports with an emphasis on the neurological signs and symptoms of carbon tetrachloride poisoning following inhalation and oral exposures. These included central nervous system effects (cerebellar degeneration, encephalomyelitis, cerebral hemorrhage) and peripheral neuritis.

Kazantzis and Bomford (1960) reported on the response of workers exposed to carbon tetrachloride vapors while cleaning quartz crystals used in electronic components. Although precise exposure data were not presented, the workers (14 men and four women, 16-54 years of age) were apparently exposed for about 8 hours/day to concentrations of approximately 67-97 ppm. Fifteen workers complained of gastrointestinal disturbances (nausea, anorexia, vomiting, flatulence, epigastric distention and discomfort), headaches, and depression. The effects were first noticed on Tuesday or Wednesday afternoons and increased in severity as the week progressed. The effects were first manifested during the preceding four months and increased in severity a few weeks before the investigation up to the point described. The cumulative exposures were apparently aggravated by window closure during the winter months. The effects described could not necessarily be attributed to acute exposure (i.e., a single 8-hr exposure) and two subjects with prior exposures presented with no signs or symptoms. The findings, however, suggest that intermittent exposures to <100 ppm over typical occupational exposure scenarios may result in notable signs of toxicity.

Groups of six male human volunteers (30-59 years of age) were subjected to carbon tetrachloride using several different exposure protocols (Stewart et al., 1961). In the first experiment, six individuals were exposed to a time-weighted-average (TWA) exposure of 49 ppm (31-87 ppm) for 70 minutes. During the exposure, all subjects noted a sweetish odor. There were no instances of eye or soft palate irritation, no nausea, and Romberg test and heel-to-toe testing remained normal. The only changes observed in clinical chemistry parameters (serum iron, serum transaminases, urinary urobilinogen, urinalysis) were a transient reduction in serum iron in two subjects during the first 48 hours after exposure, and an elevated urinary urobilinogen in one subject seven days postexposure. The study authors suggested that the depression of serum iron and elevated urine urobilinogen may have been the result of minor changes in metabolism and may be indicative of minimal liver insult. Serum enzyme activities were monitored up to seven days postexposure and remained within normal ranges. In experiment 2, six subjects were exposed to 10.9 ppm (TWA) carbon tetrachloride for 180 minutes followed by a repeat 180-minute exposure (experiment 3) to 10 ppm four weeks later. No adverse effects were reported by any of the subjects and no changes in blood pressure or timed vital capacities were detected.

Barnes and Jones (1967) reported on three cases of carbon tetrachloride poisoning; two in an industrial setting and one involving a tank truck driver delivering carbon tetrachloride. Exposure durations ranged from several minutes to approximately three hours. Signs and symptoms were typical of carbon tetrachloride poisoning and included dizziness, nausea, delirium, abdominal discomfort, oliguria. For the first case, a worker was cleaning sludge from a carbon tetrachloride tank. No respirator or other protective device was used during the 3-hour duration of the work. Soon afterward, he experienced nausea, vomiting, drowsiness, and anuria. Following medical intervention, his condition improved over several weeks. Liver biopsy revealed indications consistent with carbon tetrachloride poisoning. No exposure concentration was provided. The second case involved a worker draining a carbon tetrachloride

storage tank. The incident involved an exposure of only several minutes and produced a strong odor. By evening the worker experienced dizziness, nausea, and delirium and medical intervention was required. Simulation of the procedure resulted in carbon tetrachloride concentrations of in excess of 600 ppm. The third case involved a truck driver exposed to carbon tetrachloride during loading of the tanker. Measurement of the carbon tetrachloride levels up to 30 ppm were made at various breathing zone vicinities around the truck at the discharge end of the trip but these were made during periods of high wind and unlikely to be representative of the actual accident. Tests over 20 minutes of the breathing zones of pipe fitters at the plant where these cases occurred ranged from 30 to >600 ppm. For one case, the "main exposure level" was estimated at 210 ppm. Although all three subjects recovered, the exposures resulted in notable toxicity.

2.2.2 Epidemiologic Studies

A cross sectional study of hepatic function in workers occupationally exposed to carbon tetrachloride was conducted by Tomenson et al. (1995). In this study, multivariate analysis of liver function variables and various other hematologic and biochemical parameters were compared in 135 exposed workers and 276 non-exposed controls. Exposures were categorized based upon mean exposures; low ($\leq$1 ppm), medium (>1 ppm - 3 ppm) and high ($\geq$4 ppm). Four liver function variables (alanine transaminase, aspartate transaminase, alkaline phosphatase, and gamma glutamyl transferase) exhibited statistically significant differences from non exposed controls although there was no exposure-response relationship demonstrated. The absence of an exposure-response may have been the result of imprecision in ranking worker exposures. The biological relevance of the observed changes in serum enzyme activities was marginal and possibly of questionable clinical significance. The study authors reported that there were no clinical signs concurrent with the aforementioned changes and that a three-year follow up study at the site with the highest exposures showed no evidence of further changes in liver function variables.

2.3 Reproductive/Developmental Toxicity

Data were unavailable regarding the reproductive/developmental toxicity of acute inhalation exposure of humans to carbon tetrachloride.

2.4 Genotoxicity

No information was available regarding the genotoxicity of carbon tetrachloride in humans following inhalation exposure.

2.5 Carcinogenicity

Information regarding the potential carcinogenicity of carbon tetrachloride in humans following acute inhalation exposure are limited to two anecdotal case reports (Tracey and Sherlock, 1968). For one case, a 59-year-old man (with a history of moderate alcohol usage but not to the extent of inducing cirrhosis) died of hepatocellular carcinoma seven years following an acute exposure to carbon tetrachloride (exposure details not provided). In a second case, a 30-year-old woman died of liver cancer after 2-3 years of occupational exposure to carbon tetrachloride at concentrations sufficient to produce signs of toxicity.

The U.S. EPA has classified carbon tetrachloride as a probable human carcinogen (B2) and has established an inhalation unit risk of 1.5E-5 per $\mu g/m^3$ (U.S. EPA, 1992). The inhalation unit risk, however, was derived by route-to-route extrapolation using animal data from several sources. An assessment of carcinogenic potential following acute inhalation exposure to carbon tetrachloride was

performed (Appendix D). Acute toxicity was believed to be a more relevant determinant of AEGL values than was potential carcinogenic risk.

2.6 Summary

Case reports of human fatalities resulting from acute exposure to carbon tetrachloride are available that provide a clinical picture of dizziness, nausea, abdominal pain and oliguria/anuria with death being attributed to renal failure and hepatotoxicity. Also well documented is the potential for greater carbon tetrachloride-induced toxicity in individuals with histories of alcohol usage, a phenomenon that is consistent with the known dispositional potentiation of carbon tetrachloride toxicity by inducers of cytochrome CYP2E1 enzymes. At least one report (Norwood et al., 1950) exemplified the magnitude of this interaction by describing an exposure that produced only minor effects in two individuals while an exposure of lesser duration resulted in the death of another individual, described as a heavy drinker. Most human case reports were deficient in exposure concentrations and/or durations. Controlled exposure studies by Davis (1934) and Stewart et al. (1961) showed a varied response to inhaled carbon tetrachloride among the tested subjects. For most subjects, cumulative exposures of 30-57 ppm·hr resulted in odor detection but no irritation or clinical effects while cumulative exposures ranging from 79 to 2,133 ppm·hr produced effects ranging from nervousness and headaches to nausea and vomiting. The variability in response to carbon tetrachloride is emphasized by the fact that an estimated exposure to 63 ppm·hr was fatal in a heavy drinker while controlled exposures to 190 ppm·hr were without effect.

Quantitative data pertaining to inhalation exposures of humans to carbon tetrachloride are summarized in Table 2.

TABLE 2. EXPOSURE-RESPONSE DATA FOR HUMAN SUBJECTS ACUTELY EXPOSED TO CARBON TETRACHLORIDE

No. of Subjects	Exposure Concentration and Time	Response	Reference
6	TWA of 49 ppm (range: 31-87 ppm) for 70 minutes Ct = 57 ppm·hr	odor detection; transient decline in serum iron 20-68 hrs postexposure; elevated urine urobilinogen in one subject; no clinically significant effects and no irritation	Stewart et al. (1961)
6	TWA of 10.9 ppm (range: 10-14.2 ppm) for 180 minutes; Ct = 33 ppm·hr	odor detection; no clinically significant effects; no irritation	Stewart et al. (1961)
6	TWA of 10.1 (range: 9-14 ppm) for 180 minutes; Ct = 30 ppm·hr	odor detection; no clinically significant effects; no irritation	Stewart et al. (1961)
1	250 ppm (estimated) for 15 minutes; Ct = 63 ppm·hr	dizziness and nausea followed by renal failure and death 6 days postexposure (subject was heavy drinker)	Norwood et al. (1951)
2	250 ppm (estimated) for 4 hrs; Ct = 1,000 ppm·hr	mild headache and dizziness during exposure (non drinkers)	Norwood et al. (1951)
4	158 ppm for 30 minutes; Ct = 79 ppm·hr	nervousness in one subject, no effect in three subjects	Davis, 1934
4	76 ppm for 2 ½ hours; Ct = 190 ppm·hr	no effects	Davis, 1934
4	76 ppm for 4 hours (same subjects as above, 24 hrs later); Ct = 304 ppm·hr	no effects	Davis, 1934
3	317 ppm for 30 minutes; Ct = 159 ppm·hr	slight nausea and vomiting, headache	Davis, 1934
4	1,191 ppm for 15 minutes; Ct = 298 ppm·hr	nausea, vomiting, headache; intolerable for one subject (9-min exposure only)	Davis, 1934
3	12,800 ppm; 3-7 minutes; Ct = 640 ppm·hr	nausea, vomiting, dizziness, listlessness, headache, sleepiness	Davis, 1934
3	12,800 ppm for ≤10 minutes; Ct ≤ 2,133 ppm·hr	nausea, vomiting, sleepiness, headache	Davis, 1934
NS	5-117 ppm, 8-hr TWA; Ct = 40 - 936 ppm·hr	elevated bilirubin, restricted visual field (imprecise assessments for both)	Smyth et al., 1936

NS: not specified

3. ANIMAL TOXICITY DATA

The discussion of animal toxicity studies has been limited to acute exposure studies (<24 hrs) or longer-term studies that provided response data for exposure periods that were of possible use in the derivation of AEGL values or as a basis for comparison to AEGL values.

3.1 Acute Lethality

Lethality following acute exposures to carbon tetrachloride has been documented for laboratory species. Where available, histopathologic findings revealed hepatic injury. For some studies, data are presented that are not strictly acute exposures. Although not acute findings, some of these data may provide references point with which to evaluate draft AEGL values.

3.1.1 Nonhuman Primates

In a repeated exposure study (8 hrs/day, 5 days/week for six weeks), one of three squirrel monkeys died after the 7th exposure to 82 ppm carbon tetrachloride (Prendergast et al., 1967).

3.1.2 Rats

For a repeated exposure study of chlorinated hydrocarbons, Union Carbide (1947) conducted range-finding studies in which groups of 12 albino rats (sex not specified for range-finding study) were exposed to carbon tetrachloride for 6.5 hours (8,000 ppm), 8 hours (4,000 ppm), 8 hours (3,000 ppm) or five 8-hour exposures (1,000 ppm). Resulting mortality incidences at 14 days postexposure were 12/12, 2/12, 0/12, and 0/12, respectively.

In studies reported by Adams et al. (1952), albino rats (5-30 animals per group)were exposed to carbon tetrachloride at concentrations ranging from 3,000 - 19,000 ppm for various time periods (Table 3). One day following termination of exposure, surviving animals were killed and examined for evidence of injury. The exposures to carbon tetrachloride produced drowsiness and stupor at concentrations $\leq$4,600 ppm, loss of equilibrium and coordination at 7,300 ppm, and loss of consciousness at 12,000 and 19,000 ppm. Animals surviving 16-24 hrs after exposure to potentially lethal or near-lethal concentrations exhibited marked hepatic injury (increased serum enzyme activity, increased liver weight, lipidosis and fatty degeneration). Based on the resulting data, Adams et al. estimated that exposures of 3,000 ppm for 6-min, 800 ppm for 30-min, and 50 ppm for 7-hrs would likely be without adverse effects in rats.

Dow Chemical (1986) reported the results of acute inhalation studies in rats (age, weight, and strain not specified) exposed to carbon tetrachloride at concentrations of 10,000 or 20,000 ppm (Table 4). Lethality was 0/5, 0/5, 5/10, and 5/5 for rats exposed to 10,000 ppm for 1, 1.5, 2.0, or 2.5 hours, respectively. For rats exposed to 20,000 ppm for 0.1, 0.25, or 0.5 hours, lethality was 0/10, 5/10 and 8/10, respectively.

TABLE 3. LETHALITY IN RATS FOLLOWING ACUTE INHALATION EXPOSURE TO CARBON TETRACHLORIDE (Adams et al., 1952)

Concentration (ppm)	Duration (hrs)	Number Dead/Number Exposed
19,000	0.1	1/10
	0.2	1/5
	0.3	3/5
	0.5	2/5
	0.6	14/15
	0.7	5/5
	0.8	4/5
	1.0	9/19
	2.2	20/20
12,000	0.25	0/20
	0.5	1/10
	1.0	3/10
	2.0	7/10
	3.0	8/10
	4.0	20/20
7,300	1.0	0/20
	1.5	0/20
	2.0	1/10
	3.0	1/10
	4.0	4/10
	6.0	6/10
	7.0	4/10
	8.0	20/20
4,600	5.0	0/20
	6.0	1/11
	8.0	2/10
3,600	8.0	4/20
	12.0	1/10
3,000	8.0	0/20
	10.0	1/30

TABLE 4. LETHALITY IN RATS FOLLOWING ACUTE INHALATION EXPOSURE TO CARBON TETRACHLORIDE (Dow Chemical (1986)

Concentration (ppm)	Duration (hrs)	Number Dead/ Number Exposed
10,000	1.0	0/5
	1.5	0/5
	2.0	5/10
	2.5	5/5
20,000	0.1	0/10
	0.25	5/10
	0.5	8/10

3.1.3 Mice

Svirbely et al. (1947) reported lethality data for mice exposed to carbon tetrachloride. In the experiments described, groups of 20 Swiss mice (20 g; gender not specified) were exposed to carbon tetrachloride vapors for eight hours. The concentrations were calculated by dividing the amount of carbon tetrachloride volatilized during the eight-hour exposure by the volume of air that flowed through the chamber. The concentrations were confirmed by chemical analysis. The results are shown in Table 5.

TABLE 5. LETHALITY IN MICE EXPOSED TO CARBON TETRACHLORIDE FOR EIGHT HOURS

Concentration (ppm)	Mortality
6,340	0/20
7,628	2/20
8,088	19/20
8,787	10/20
9,327	20/20

Svirbely et al. (1947)

In a pilot study conducted at (Dow Chemical, 1986), 8,500 ppm was found to be an 11.5-hr LC_{50} for female Swiss-Webster mice. The lethality response of mice appeared to be biphasic. The study author reported two LCt_{50} values (680 and 850 minutes) for the steep exposure-response curve.

The lethal response of mice (strain and gender not specified) to a 3.5 minute inhalation exposure to carbon tetrachloride was provided by Merck and Co. in a report to the EPA Office of Toxic Substances (Merck, 1983). For mice exposed to 150,000, 75,000, 37,500, 18,800, or 9,400 ppm, lethal responses (no. fatalities/no. exposed) were 6/6, 2/6, 0/5, 0/5, and 0/5, respectively. No additional details were provided.

3.1.4 Guinea Pigs

In a repeated exposure study (8 hrs/day, 5 days/week for six weeks), three of 15 guinea pigs died on the 20th, 22nd, and 30th day of exposure to 82 ppm carbon tetrachloride (Prendergast et al., 1967). Histopathologic findings in the liver were consistent with carbon tetrachloride-induced hepatotoxicity. Data for times frames that would be appropriate for AEGL derivations were not provided.

In addition to rats (see Section 3.1.3), Dow Chemical (1986) also reported the results of acue inhalation studies in guinea pigs exposed to carbon tetrachloride at concentrations of 10,000 or 20,000 ppm (Table 6). Lethality was 0/5, 1/10, 4/5, 1/5, and 1/5 for guinea pigs (age, weight, and strain not specified) exposed to 10,000 ppm for 1, 1.5, 2.0, 2.5, or 3.0 hours, respectively. For exposure to 20,000 ppm for 0.25, 0.5, or 1.0 hours, lethality was 0/5, 2/5 and 4/5, respectively.

TABLE 6. LETHALITY IN GUINEA PIGS FOLLOWING ACUTE INHALATION EXPOSURE TO CARBON TETRACHLORIDE

Concentration (ppm)	Duration (hrs)	Number Dead/ Number Exposed
10,000	1.0	0/5
	1.5	1/10
	2.0	4/5
	2.5	1/5
	3.0	1/5
	0.25	0/5
20,000	0.5	2/5
	1.0	4/5

Dow Chemical (1986)

3.1.5 Rabbits

A single rabbit was exposed to 20 mg carbon tetrachloride/L (3,178.6 ppm) three hours per day for three days. The rabbit died on the fifth day with necropsy revealing pulmonary, renal, and hepatic involvement (Davis et al., 1934).

3.1.6 Summary of Lethal Toxicity In Animals

Quantitative data regarding the lethality of carbon tetrachloride following acute inhalation exposure are available for several laboratory species (rats, mice, and guinea pigs). Limited data are available for nonhuman primates and dogs.

3.2 Nonlethal Toxicity

3.2.1 Nonhuman Primates

A subchronic exposure study by Smyth et al. (1936) reported little harm to groups of four rhesus monkeys exposed to 50 or 200 ppm carbon tetrachloride, 8 hrs/day, 5 days/week for 10 ½ months. Liver damage (slight fatty degeneration) was detected but resolved 28 days following cessation of exposure. No data were provided that were specific for acute exposure times frames.

3.2.2 Dogs

In a study submitted to the Office of Toxic Substances by Union Carbide (Union Carbide, 1947), a mongrel dog was exposed to carbon tetrachloride (400 ppm), 7 hours/day for six months. The dog did not die but exhibited a significant decrease in body weight relative to unexposed controls.

3.2.3 Rats

In a subchronic inhalation exposure study, groups of albino rats (21-25) exposed to carbon tetrachloride (50, 100, 200, or 400, ppm), 8 hrs/day, 5 days/week for 10 ½ months resulted in both liver and kidney damage but, with the exception of two rats in the 400-ppm group, was not severe enough to compromise what the investigators termed as adequate function (Smyth et al., 1936). Data specific to acute exposure periods were not provided.

In addition to lethality data, Adams et al. (1952) also provided data pertaining to nonlethal exposures of rats to carbon tetrachloride. For this phase of the study, groups of three or four male albino rats were exposed to carbon tetrachloride using various protocols (3 to 420 minutes) to determine the maximum exposure without overt signs of toxicity. Toxicity endpoints evaluated included changes in liver weight, alterations in total lipid content of the liver, and gross and microscopic evidence of fatty degeneration. The results are summarized in Table 7. It must be noted that the no-effect responses identified in this study are based upon endpoints characteristic of notable hepatic damage and that an evaluation of more sensitive endpoints (e.g., serum enzyme activities) probably would have detected a toxic response at lower concentrations or exposure durations.

Cornish and Block (1960) exposed male and female Sprague-Dawley rats to carbon tetrachloride (50, 100, 250, 1000 or 1500 ppm) for four hours. Exposure concentrations were found to be within 10% of the calculated target concentrations. Twenty-four hours after a single 4-hour exposure to 1500 ppm, SGOT and xanthine oxidase activities were increased 750% and 250%, respectively, relative to controls (Table 8). Males and females responded similarly at the 1500 ppm exposure. The serum enzyme activities returned to normal five days after the exposure. Twenty-four to 48 hours after exposure to 1,000 ppm, SGOT and xanthine oxidase in was increased 275% and 180%, respectively for males and 800% and 285% in females. For the 250 ppm groups at 24 hours, SGOT in males was 160%; xanthine oxidase was unaffected. For females, SGOT was 250% and xanthine oxidase was 135% greater than unexposed controls. At 50 and 100 ppm, no significant changes in these enzyme activities were noted.

TABLE 7. NONLETHAL RESPONSE OF RATS EXPOSED TO CARBON TETRACHLORIDE USING VARIOUS EXPOSURE PROTOCOLS

Concentration (ppm)	Exposure duration (min) No adverse effect[a]	Exposure duration (min) Adverse effect[a]
12,000	-	3
3,000	6	9
800	30	60
400	-	60
100	-	420
50	420	-

Adams et al., 1952

[a] Adverse effects characterized by alteration in liver weight, total lipid content of the liver, and gross and microscopic changes in the liver.

The relationship between exposure time and exposure concentration was examined by David et al., (1981) (Table 8). In these experiments, serum glutamic pyruvate transaminase (SGPT) activity was used to assess the toxic response of male Wistar rats (12 per group) subjected to various exposure protocols that provided identical cumulative exposures (Ct = 300 ppm·hr). The protocols included 72-min exposure to 250 ppm, 6-hr exposure to 50 ppm, six 3-min exposures to 1,000 ppm at 1-hr intervals, and 18-min at 1,000 ppm. Groups of 12 rats serving as controls were exposed to clean air. Even though the cumulative exposure was the same for all protocols, it was found that exposures to greater concentrations of short duration resulted in greater elevation of serum SGPT than did exposures to lower concentrations for longer durations (Table 7). Histological examination of the carbon tetrachloride-exposed rats revealed mild changes (mild steatosis, mild hydropic degeneration) in the liver that were not qualitatively different among the exposure groups. The study authors concluded that, based upon their findings, the concentration of carbon tetrachloride in the blood and liver are more important than the total amount of carbon tetrachloride absorbed.

TABLE 8. EFFECTS OF EXPOSURE PROTOCOL ON SGPT AND XANTHINE OXIDASE ACTIVITY IN RATS EXPOSED TO CARBON TETRACHLORIDE

Exposure	Xanthine oxidase (% of control)	SGPT or SGOT (U/L or % of controls)
50 ppm; 4 hrs[a]	no effect	no effect
100 ppm; 4 hrs[a]	no effect	no effect
250 ppm; 4 hrs[a]	males; marginal females; 135%	marginal; males females; 250%
1000 ppm; 4 hrs[a]	males: 180% females: 285%	males; 275% females: 800%
1500 ppm; 4 hrs[a]	males; 250% females; 250%	750% males 750% females
Controls[b]	NA	50
250 ppm for 72 min[b]	NA	60
50 ppm for 6 hrs[b]	NA	50
1,000 ppm for 18 min[b]	NA	95
1,000 ppm (six 3-min exposures at 1-hr intervals)[b]	NA	40

NA: not applicable (not examined)
[a]Cornish et al., 1960 (SGOT monitored); [b]David et al., 1981 (SGPT monitored)

Appelman et al. (1985) conducted a series of experiments in which groups of 10 male Wistar rats were exposed 6 hrs/day, 5 days/week for four weeks to carbon tetrachloride vapor. Daily exposure regimens varied and included: 6-hr exposures (63 and 80 ppm), two 3-hr exposures (63 and 80 ppm) with 1.5-hr interruption, two 3-hr exposures (63 and 80 ppm, at 1.5-hr intervals) with 5-min peaks equivalent to six times the base exposure. Controls were exposed to fresh air. With the exception of body weight data that were taken at weekly intervals, data were available only for the 4-week period. No overt signs of toxicity were detected in the treated rats. Serum enzyme activities (SGOT, SGPT) following the 4-week exposures were significantly elevated (2-9 fold) in all treatment groups, and microsomal protein content and some microsomal enzyme activity levels were significantly reduced following treatment. This study provided data showing measurable evidence of reversible toxic effects following various regimens of inhalation exposure to 63 or 80 ppm carbon tetrachloride over a 4-week period. The available data were not appropriate for AEGL-specific time frames or for extrapolation to AEGL time frames.

In an extensive study to evaluate the effect of exposure regimen on the distribution and toxicity of carbon tetrachloride, Paustenbach et al. (1986b) exposed groups of male Sprague-Dawley rats (4/group) to 100 ppm carbon tetrachloride for 8 or 11.5 hrs/day for 1 to 10 days. For toxicity determination, serum sorbitol dehydrogenase (SDH) activity was measured. Results of the 1-day exposures showed that SDH

was slightly higher ($p<0.05$) in rats of the 11.5-hr group (14.8±3.7 IU/ml) relative to those in the 8-hr group (7.0±1.5 IU/ml). SDH activity in control rats was 8.5±2.0 IU/ml. SDH activity increased only ≈2.5 to 3.5-fold (21.0±3.3 IU/ml for 8 hr/day; 29.0±6.2 IU/ml for 11.5 hr/day) with exposure durations of 3 days. Histopathologic evaluation was limited to 1 and 2-week exposures and not available for the shorter exposures.

In studies to examine the effect of route and pattern of exposure on the pharmacokinetics and acute toxicity of carbon tetrachloride, Sanzgiri et al. (1995) exposed male Sprague-Dawley rats (325-375 g) to carbon tetrachloride (100 or 1,000 ppm) for two hours. The total internal dose (i.e., systemically absorbed dose) over the 2-hour exposure was determined to be 17.5 and 179 mg/kg, respectively. Relative to unexposed controls, a 2-hr exposure to 100 ppm resulted in no biologically relevant alterations in serum sorbitol dehydrogenase (SDH) or serum alanine aminotransferase (ALT) activity but did significantly reduce hepatic microsomal P450 and glucose-6-phosphatase (G6Pase) levels. Following a 2-hr exposure to 1,000 ppm, both serum SDH (87.9±25.7 mU/ml vs 5.2±1.0 mU/ml for controls; $p\leq0.05$) and ALT activities (53.3±14.7 mU/ml vs 24.4±2.2 mU/ml for controls; $p\leq0.05$) were significantly increased, microsomal P450 activity significantly decreased (0.61±0.04 vs 0.81±0.02 for controls), and G6Pase activity was unchanged.

Wang et al. (1997) studied the effects of dose and route of administration on the metabolism and toxicity of carbon tetrachloride. In this study, groups of five Wistar rats were exposed to carbon tetrachloride (50 or 500 ppm) for six hours. Chamber concentrations were monitored every 15 minutes (gas chromatograph with hydrogen flame ionization detector). As determined by serum glutamic-oxaloacetic acid transaminase (SGOT) and glutamic pyruvic transaminase (SGPT) activity, exposure of rats to 50 ppm resulted in no hepatic damage although exposure to 500 ppm resulted in statistically significant elevations indicative of minor hepatic injury (SGOT: 29, 33, and 57 IU/L for controls, 50 ppm, and 500 ppm, respectively; SGPT: 20, 20, and 38 IU/L for controls, 50 ppm, and 500 ppm, respectively). Rats pretreated with ethanol (2 g/rat/day) for three weeks exhibited substantially greater evidence of hepatic damage based upon SGOT and SGPT activity (SGOT: 31, 62, and 1720 IU/L; SGPT: 18, 41, and 870 IU/L for ethanol controls, 50 ppm, and 500 ppm, respectively).

3.2.4 Mice

In addition to lethality endpoints (Section 3.2.4), the study conducted at Dow Chemical (Gehring, 1987) also examined nonlethal endpoints of anesthesia and SGPT activity. At an exposure concentration of 8,500 ppm, an ECt_{50} of ≈0.16 minutes was determined for SGPT activity and an ECt_{50} of ≈21 minutes for anesthesia effects.

Belyaev et al. (1992) conducted experiments to assess fibroblast growth in the livers of male A/He mice following carbon tetrachloride exposure. Centrilobular necrosis encompassing 1/5 to 1/3 of the lobule was observed at twenty-four hours after a single 4-hour exposure to 30 mg/L (30,000 mg/m^3 or 4,770 ppm). Continued biweekly exposures ultimately resulted in fibrosis and cirrhosis. No animal deaths were reported.

3.2.5 Rabbits

Data on the nonlethal effects of inhalation exposure of rabbits to carbon tetrachloride are limited to a study by Ugazio et al. (1995). Primarily a subchronic exposure for the development of a model for cirrhosis, the exposure protocol consisted of 2-hour exposures of male New Zealand white rabbits, twice per week, to carbon tetrachloride concentrations of 100 ppm which were subsequently increased to 600 ppm by 23 weeks. Although daily exposure results were not provided, none of the 12 rabbits died. By

week 4, however, there was a 300% increase in hexobarbital sleeping time implying a decrease in hepatic microsomal enzyme activity, and laparotomy revealed initial signs of hepatic fibrosis.

3.2.6 Cats

Wong and DiStefano (1966) conducted inhalation exposure experiments on anesthetized cats. Cats of both sexes, anesthetized with sodium pentobarbital, were exposed via a tracheal cannula to carbon tetrachloride concentrations of 10,000 ppm for 15, 30, 60, or 240 minutes. Controls were treated similarly but with no carbon tetrachloride exposure. The kidney weight-to-body weight ratio was significantly increased ($p<0.05$) following 60 and 240-minute exposures, and adrenal weight-to-body weight ratios were significantly increased ($p<0.05$) for the 30, 60, and 240-minute exposures. Liver weight-to-body weight ratios were unaffected by the treatment. Total lipid content in the renal cortex increased after 15 minutes of exposure but was not further increased with longer exposures. The elevated total lipids were still evident at 12 hours postexposure but were lower than baseline values at 24 hours. Lipid content in the adrenal glands and liver were unaffected. With the exception of lipid accumulation, there were no significant histologic findings in the kidneys, and there were no histologic changes in the adrenal glands. Central necrosis was observed in the liver 12 hours after the 240-minute exposure; this became more prevalent at 24 hours postexposure. The results of this study affirm the liver and kidneys as target organs for carbon tetrachloride toxicity but also suggest that the kidneys may be affected earlier than the liver. It is uncertain whether or not the effects observed would have progressed to lethality.

3.2.7 Summary of Nonlethal Toxicity In Animals

Table 9 summarizes the nonlethal effects in animals following inhalation exposure to carbon tetrachloride. Although data pertaining to acute exposures is the primary focus, longer-term exposures with observations at 24 hours or less are included as well as longer-term exposures that may provide useful perspective in assessing the effects of inhalation exposure to carbon tetrachloride. Generally, the concentration of carbon tetrachloride appears to be the driver for severity of effects. The liver and kidneys appear to be primary targets for toxicity. Serum enzyme activity levels are routinely employed as biochemical indices of this toxicity and serve as reliable indicators of hepatic damage although a progression of injury may occur after cessation of exposure. The toxic response to carbon tetrachloride among the various species tested appears to vary.

TABLE 9. NONLETHAL EFFECTS OF CARBON TETRACHLORIDE IN LABORATORY SPECIES FOLLOWING INHALATION EXPOSURE

Species	Exposure	Effect	Reference
Rhesus monkey	200 ppm, 8 hrs/day, 5 days/week for 10.5 mos	transient hepatic injury	Smyth et al., 1936
Dog	400 ppm, 7 hrs/day for 6 mos.	decreased body weight	Union Carbide, 1947
Rat	1500 ppm, varying exposure profiles all with Ct=4500 ppm·hr	hepatic vacuolation and individual cell necrosis which varied with exposure profile	Van Stee et al., 1982
	200 ppm, 8 hrs/day, 5 days/week for 10.5 mos.	no significant effects	Smyth et al., 1936
	50 ppm, 6 hrs for 13-18 days	minor increase in SGPT, minor histological changes in the liver	David et al., 1981
	250 ppm, 72 min for 13-18 days	minor increase in SGPT, minor histological changes in the liver	David et al., 1981
	1,000 ppm, 18 min for 13-18 days	minor increase in SGPT, minor histological changes in the liver	David et al., 1981
	1,000 ppm (six 3-min exposures with 1-hr intervals)	minor increase in SGPT, minor histological changes in the liver	David et al., 1981
	63 ppm, 6 hrs/day, 5 days/week for 4 weeks	transient hepatic effects; 2 to 9-fold increase in SGOT, SGPT	Appelman et al., 1985
	80 ppm 6 hrs/day, 5 days/week for 4 weeks	transient hepatic effects; 2 to 9-fold increase in SGOT, SGPT	"
	63 ppm (two 3-hr exposures, 1.5 hr intervals)	transient hepatic effects; 2 to 9-fold increase in SGOT, SGPT	"
	80 ppm (two 3-hr exposures, 1.5 hr intervals)	transient hepatic effects; 2 to 9-fold increase in SGOT, SGPT	"
	63 ppm (two 3-hr exposures, 1.5 hr intervals, 5-min peaks of 6-fold baseline)	transient hepatic effects; 2 to 9-fold increase in SGOT, SGPT	"
	80 ppm (two 3-hr exposures, 1.5 hr intervals, 5-min peaks of 6-fold baseline)	transient hepatic effects; 2 to 9-fold increase in SGOT, SGPT	"
	100 ppm, 8 hrs	no significant effect on SDH	Paustenbach et al., 1998b
	100 ppm 11.5 hrs	marginally increased SDH	"
	180 ppm, 15 min	"comatose"; increased ALT at 24 hrs postexposure	Sakata et al., 187
	100 ppm, 2 hrs	no biologically relevant effect	Sanzgiri et al., 1995
	1,000 ppm, 2 hrs	increased ALT and SDH, decreased P-450	"
	50 ppm, 6 hrs	no effect	Wang et al., 1995
	500 ppm, 6 hrs	minor increase in SGOT and SGOT	"

TABLE 9. (Cont.) NONLETHAL EFFECTS OF CARBON TETRACHLORIDE IN LABORATORY SPECIES FOLLOWING INHALATION EXPOSURE

Species	Exposure	Effect	Reference
Rat	12,000 ppm, 3 min	altered liver weight, total lipid content and/or gross or microscopic changes in the liver	Adams et al., 1952
	3,000 ppm, 6 min 3,000 ppm, 9 min	no effect altered liver weight, total lipid content and/or gross or microscopic changes in the liver	Adams et al., 1952
	800 ppm, 30 min 800 ppm, 60 min	no effect altered liver weight, total lipid content and/or gross or microscopic changes in the liver	Adams et al., 1952
	400 ppm, 60 min	altered liver weight, total lipid content and/or gross or microscopic changes in the liver	Adams et al., 1952
	100 ppm, 420 min	altered liver weight, total lipid content and/or gross or microscopic changes in the liver	Adams et al., 1952
	50 ppm, 420 min	no effect	Adams et al., 1952
Mouse	8,500 ppm, 0.16 min	ECt_{50} for SGPT activity	Gehring, 1987
	8,500 ppm, 21 min	ECt_{50} for anesthesia	
Rabbit	100 ppm, 2 hrs/week for 23 weeks (increased to 600 ppm by 23 weeks)	increased hexobarbital sleeping time; hepatic fibrosis	Ugazio et al., 1995
Cat	10,000 ppm (via tracheal cannulation) for 15, 30, 60, or 240 minutes	increased total lipids in renal cortex at 15 min; increased relative adrenal wt. ≥15 to 30 min; central necrosis in liver at 240 min	Wong and DiStefano, 1966

3.3 Developmental/Reproductive Toxicity

In a study reported by Schwetz et al. (1974), groups of pregnant Sprague-Dawley rats were exposed for 7 hrs/day on days 6-15 of gestation to carbon tetrachloride at nominal concentrations of 300 or 1,000 ppm (analytical concentration of 334 and 1,004 ppm, respectively). Exposed rats exhibited no overt signs of toxicity although reduced food consumption (and consequent decreased body weight gain) and signs of hepatotoxicity (increased SGPT activity, pale, mottled livers, increased relative liver weight) were evidence of maternal toxicity in both exposure groups. Signs of maternal toxicity were resolved by six days postexposure. Exposure to carbon tetrachloride had no effect on conception rate, number of implantations, or litter size. A summary of fetal anomalies is shown in Table 10. Relative to unexposed controls, the only statistically significant findings were values were for total skeletal anomalies (300 ppm only), sternebral anomalies (1,000 ppm only), and subcutaneous edema (300 ppm only). The investigators concluded that exposure to carbon tetrachloride under the conditions of this study was not teratogenic to the developing embryo. However, there was evidence of fetotoxicity as determined by decreased crown-rump length and fetal body weight in the exposed group compared to the controls.

TABLE 10. INCIDENCES OF FETAL ANOMALIES IN RATS FOLLOWING INHALATION EXPOSURE TO CARBON TETRACHLORIDE[a]

	Control	300 ppm	1000 ppm
Number of litters examined	43	22	22
Gross anomalies	0	0	0
Skull anomalies (delayed ossification)	12(5)	9(2)	9(2)
Lumbar ribs or spurs	24(10)	41(9)	27(6)
Vertebral anomalies (bipartite centra)	21(9)	27(6)	14(3)
Sternebral anomalies (bipartite; delayed ossification)	61(14) 11(2)	68(15)	59(13)[b]
Total skeletal anomalies	58*25)	91(20)[b]	68(15)
Subcutaneous edema	33(14)	59(13)[b]	50(1)
Dilated ureters	12(5)	14(3)	5(1)
Total soft tissue anomalies	51(22)	68(15)	59(13)

[a] Values presented as percent of litters affected (no. of litters)
[b] Significantly different from control ($p < 0.05$, Fisher Exact Probability test)

3.4 Genotoxicity

Data regarding the genotoxicity of carbon tetrachloride are equivocal. Although DNA adducts have been identified in a variety of studies, no specific adducts were characterized (McGregor and Lang, 1996). Using Chinese hamster ovary cells, carbon tetrachloride at 1,270 μg/ml was negative in sister chromatid exchange and chromosomal aberration tests both with and without activation (Loveday et al., 1990). Recombination effects have been reported in Saccharomyces cerevisiae and Aspergillus nidulans (reviewed in McGregor and Lang, 1996). Reverse mutation tests using several strains of Salmonella typhimurium were negative (McGregor and Lang, 1996).

Mirsalis and Butterworth (1980) reported no unscheduled DNA synthesis in hepatocytes from rats pretreated with carbon tetrachloride.

Studies with radiolabeled carbon tetrachloride indicated binding to DNA and rRNA in rat liver of animals pretreated with 3-methylcholanthrene (Rocchi et al., 1973), and Sawada et al. (1989) indicated that carbon tetrachloride (200 mg/kg) caused 23-fold increase in replicative DNA synthesis at 48 hours.

3.5 Carcinogenicity

Data regarding tumorigenic responses to carbon tetrachloride following inhalation exposure were limited. Costa et al. (1963) reported the occurrence of liver tumors following repeated inhalation exposure of 30 rats (age, sex, strain not reported) to carbon tetrachloride (concentration and daily exposure protocol not specified). The exposure duration was seven months followed by a three to nine-month observation period. Ten of the rats exhibited lesions of the liver characterized histologically as adenocarcinomas, trabecular carcinomas, and anaplastic carcinomas accompanied by cirrhosis. The malignant nature of the tumors was affirmed by the invasion of hepatic veins by hepatoma cellular elements.

Liver tumors have been reported for rats and mice following subcutaneous injection (Reuber and Glover, 1979) and gavage administration (Edwards, 1941; Edwards and Dalton, 1942; Edwards et al., 1942; Andervont, 1958; Weisburger, 1977). Because of the possible differences in metabolism and disposition for different routes of administration, and the resulting differences in target organ/tissue dose, and the chronic exposure durations, these data are inappropriate for assessing carcinogenic potential of acute inhalation exposures.

In studies with rat liver microsomal preparations, Castro et al. (1997) reported that free radicals ($\cdot CCl_3$, $CCl_3O_2\cdot$, $\cdot OH$) were capable of altering the DNA bases, guanine, cytosine and thymine. The authors contended that if these altered bases were formed and not adequately repaired before cell replication, liver DNA could be adversely affected and that such processes may be involved in carbon tetrachloride-induced carcinogenicity.

Based upon sufficient evidence in animals, the U.S.EPA (1992) has classified carbon tetrachloride as a possible human carcinogen and lists an inhalation unit risk of 1.5E-5/$\mu g/m^3$ based upon oral administration data. Carbon tetrachloride is classified as a Group 2B (possibly carcinogenic to humans) carcinogen by IARC and the NTP reasonably anticipates it to be a human carcinogen.

3.6 Summary

Animal toxicity data for inhaled carbon tetrachloride affirm hepatotoxic and renal effects, as well as anesthetic-like effects, as primary endpoints. These findings are consistent with those for human exposures, although carbon tetrachloride-induced nephrotoxicity appears to be more prevalent in humans than in laboratory species. The most sensitive endpoint for evaluating the toxicity of carbon tetrachloride in animals appears to be measurement of serum enzyme activities that reflect tissue damage. Several studies have provided lethality data for various concentrations and exposure durations. Data for nonlethal effects are also available but are much more limited or come from studies that reported effects only after long-term exposures to low concentrations (generally <200 ppm).

4. SPECIAL CONSIDERATIONS

4.1 Metabolism and Disposition

Carbon tetrachloride is metabolized by the mixed function oxidases of the liver (Sipes et al., 1977) as well as other organs such as the adrenal glands (Colby et al., 1994). Known metabolites include carbon dioxide, chloroform, free radicals, and possibly hexachloroethane (Recknagel, 1967; Glende, 1972; Paustenbach et al., 1988). Additional, unidentified metabolites are excreted in the feces and urine (McCollister, et al., 1951; Paustenbach et al., 1986a).

Based upon limited data from human subjects, Stewart et al. (1961) found that the carbon tetrachloride elimination via expired air is inversely related to the duration of exposure.

The absorption, distribution and excretion of [^{14}C]-carbon tetrachloride was studied in female rhesus monkeys (McCollister et al., 1951). The monkeys breathed from bags containing 50 ppm [^{14}C]-carbon tetrachloride and exhaled via a valve system into exhale bags both of which were impermeable to air and carbon tetrachloride for the duration of the experiments. Duration of exposure was 139, 300, or 344 minutes. The average rate of absorption was found to be 0.022 mg/kg/min with an average absorption of 30% of the amount inhaled. Tissue analysis revealed that most of the carbon tetrachloride was in adipose tissue (tissue:blood ratio = 7.94). Radioactivity was found in the blood, exhaled carbon dioxide, urinary urea and carbonate, and feces. It was estimated that at least 51% of the absorbed radioactivity had been eliminated within 180 minutes of exposure. Dermal exposure to vapors (485 ppm for 240 minutes and 1,150 ppm for 270 minutes) revealed negligible absorption as determined by radioactivity in the blood and expired air.

Based upon limited data from humans, Lehmann and Schmidt-Kehl (1936) estimated pulmonary absorption to be about 60% for exposures to 50 ppm, or about twice that observed from non human primates (McCollister et al., 1951).

Paustenbach et al. (1986a) reported differences in the distribution and elimination of inhaled carbon tetrachloride relative to exposure regimen. In this study, Sprague-Dawley rats were exposed to 100 ppm carbon tetrachloride for either 8 hrs/day or 11.5 hrs/day. The daily exposure regimens were adjusted such that cumulative exposures were identical. Following 2-week exposure to the 11.5 hr/day schedule, [^{14}C]-carbon tetrachloride in the breath and ^{14}C activity in the feces represented 32% and 62% of the total dose respectively. For the 8 hr/day exposure, expired [^{14}C]-carbon tetrachloride and fecal ^{14}C represented 45% and 48% of the total dose, respectively, demonstrating that fecal excretion was more prevalent in the 11.5-hr exposure schedule. Regardless of the exposure schedule, urinary excretion and ventilatory elimination of $^{14}CO_2$ was minimal (8% and 2%, respectively). Results of the study indicated that >60% of the inhaled dose was metabolized and that the 11.5-hr/day schedule resulted in greater accumulation of carbon tetrachloride in the poorly perfused lipophilic depots such as adipose tissue. Overall, results of this study suggest that relatively small changes in exposure regimens may influence the rate and route of elimination of carbon tetrachloride.

A physiologically-based pharmacokinetic (PBPK) model for inhaled carbon tetrachloride was developed by Paustenbach et al. (1988) that provided V_{max} (0.65 mg/kg/hr) and K_m (0.25 mg/L) based upon exposures of Sprague-Dawley rats to 100 ppm. Metabolites were partitioned into three compartments: those excreted in the breath (CO_2 and possibly hexachloroethane), urine, and feces. Results of simulations with the model were consistent with the human data of Stewart et al. (1961) and the monkey data reported by McCollister et al. (1951).

Although McCollister et al. (1951) reported measurable amounts of radioactivity in the feces of monkeys exposed to [^{14}C]-CCl_4 via inhalation and Paustenbach et al. (1986) reported fecal excretion in rats, Page and Carlson (1994) found that fecal elimination of carbon tetrachloride (as parent compound) by Sprague-Dawley rats did not significantly contribute to overall elimination of carbon tetrachloride following single or repeated inhalation exposure. The authors contended it was more likely that the minimal fecal elimination represents a very slow elimination of a metabolite or catabolic product of a carbon tetrachloride-macromolecular adduct.

Kinetic parameters were estimated for rats exposed to 100 or 1,000 ppm carbon tetrachloride for two hours (Sanzgiri et al., 1995). There were no significant differences in the $t_{½}$ (162 and 166 min., respectively), or the apparent clearance (148 and 100 ml/min/kg, respectively). However, as would be expected, the area under the curve (AUC) was proportionately greater for the 1,000 ppm (1,885 μg·min/ml) exposure compared to the 100 ppm (124 μg·min/ml) as was the C_{max} (1.0 and 12.8 μg/ml, respectively).

The effect of exposure route on the disposition of carbon tetrachloride in rats was examined by Sanzgiri et al. (1997). Briefly, a comparison of uptake, distribution, and elimination of carbon tetrachloride following inhalation (1,000 ppm for 2 hrs) or oral exposure (179 mg/kg, single bolus or 2-hr oral infusion) was conducted in male Sprague-Dawley rats. Carbon tetrachloride tissue levels were lower in the gastric infusion groups than in the oral bolus or inhalation exposure group. In fact, based upon AUC data (0-24 hrs), liver accumulation (and most tissues) of carbon tetrachloride was higher following inhalation exposure (2,823 μg·min/ml), than following oral bolus (1,023 μg·min/ml) or oral infusion (149 μg·min/ml). As would be expected for a lipid-soluble chemical, the tissue-specific time courses for uptake and elimination were determined largely by the perfusion rate and lipid content of the tissue. The study authors concluded that the most appropriate measure of internal dose for carbon tetrachloride-induced acute hepatotoxicity is the tissue concentration versus time curve from 0 to 30 minutes.

4.2 Mechanism of Toxicity

Pulmonary, hepatic, cardiovascular, hematological, and central nervous system toxic responses have been documented for inhalation exposure of humans and/or laboratory species to carbon tetrachloride. However, the liver and kidneys appear to be the primary targets for carbon tetrachloride toxicity. The majority of research on mechanism of action has focused on hepatotoxic processes.

The mechanism of carbon tetrachloride hepatotoxicity has been extensively studied (see reviews by Zimmerman, 1978 and Clawson, 1989). Because the great volume of data available on this topic, an in-depth discussion is beyond the scope of this document. Briefly, the metabolism of carbon tetrachloride is mediated by ethanol-inducible CYP2E1. The hepatotoxicity of carbon tetrachloride appears to be mediated by reactive metabolites. Several reactive metabolites have been implicated in the mechanism(s) and include the trichloromethyl and chlorine free radicals (Rechnagel and Glende, 1973), the trichloromethylperoxy free radical (Slater, 1982), carbenes (Reiner and Uehleke, 1971), and the carbon dioxide anion radical (LaCagnin et al., 1988). The trichloromethyl free radical, resulting from homolytic cleavage of the carbon-chlorine bond is thought to react with fatty acids in the endoplasmic reticulum membranes which form secondary free radicals resulting in lipid peroxidation. The process rapidly becomes autocatalytic and results in further peroxidation thereby explaining the toxic potency of carbon tetrachloride. Rao and Recknagel showed that incorporation of ^{14}C from [^{14}C]-carbon tetrachloride into rat liver microsomal and mitochondrial lipids was rapid ($\approx$5 minutes) following oral administration of carbon tetrachloride. Slater hypothesizes that the trichloromethylperoxy free radical, which is even more reactive, interacts with unsaturated membrane lipids resulting in lipid peroxidation. Ultimately, the lipid peroxidation from either of these mechanisms leads to cellular degeneration. Alternately, the involvement of carbenes and their mediation of covalent binding of macromolecules has also been proposed as has been the carbon dioxide anion radical involvement. These processes ultimately result in centrilobular necrosis and fatty degeneration of the liver. Glende and Recknagel (1991) reported on the involvement of carbon tetrachloride-activated phospholipase A2 and the role of increased intracellular calcium in hepatocyte injury.

In addition to hepatotoxicity, carbon tetrachloride is also known to affect the central nervous system (Stevens and Forster, 1953; Cohen, 1957). The narcotic properties of carbon tetrachloride are well documented (ATSDR, 2003) but the precise mechanism of action is unknown.

4.3 Structure-Activity Relationships

Assessment of structure-activity relationships were not instrumental is deriving AEGL values for carbon tetrachloride.

4.4 Other Relevant Information

4.4.1 Species and Strain Variability

Johnson and Simmons (1994) reported on the variable susceptibility to carbon tetrachloride-induced hepatotoxicity between Fischer-344 and Sprague-Dawley rats. Briefly, following gavage administration of 0.1 or 0.4 ml/kg, it was found that Sprague-Dawley rats were more resistant to carbon tetrachloride-induced hepatic necrosis than were Fischer-344 rats.

It has also been reported that rats eliminate CCl_4 faster than larger species (Andersen, 1981) such as monkeys (McCollister et al., 1951) and humans (Stewart et al., 1961) and that rat studies may underestimate the accumulation of CCl_4 in tissues of humans.

One toxic endpoint that occurs consistently among species is hepatotoxicity. Mild signs of hepatotoxicity, such as elevated serum enzyme activities, have been reported in both humans and rodents. Interspecies comparisons of this endpoint can be made by examining the exposure associated with producing the effect in each species. The study by Stewart et al. (1961) reported minor enzymatic changes in two of six human subjects exposed to 49 ppm for 70 minutes. In contrast, rats exhibited mild elevations in serum enzyme activities following exposures to 250 ppm for four hours (Cornish and Block, 1960) and 250 ppm for 70 minutes (David et al.,1981). Using these similar responses among species as a reference point, one can compare the relative susceptibility using exposures on a ppm · min or $ppm^{2.5}$ · min basis (Table 11). For carbon tetrachloride, the appropriate exposure term appears to be of the form, $ppm^{2.5}$ · min. The range of human-to-rat variability is 5- to 200-fold for the serum enzyme activity endpoint. This endpoint, however, is known to exhibit inherent variability.

TABLE 11. COMPARATIVE EXPOSURES OF CARBON TETRACHLORIDE PRODUCING MINOR CLINICAL CHEMISTRY CHANGES

Species	Exposure	Cxt (ppm · min)	Cxt ($ppm^{2.5}$ · min)	Reference
Human	49 ppm, 70 min	3430	1,176,490	Stewart et al., 1961
Rat	250 ppm, 4 hrs	60,000	237,170,824	Cornish and Block, 1960
Rat	250 ppm, 70 min	17,500	10,249,085	David et al., 1981
Interspecies variability		5-17 fold	9-200 fold	

As discussed earlier, the metabolism of carbon tetrachloride is mediated by the mixed function oxidase, CYPIIE1. The hepatotoxicity of carbon tetrachloride appears to be mediated by reactive intermediates resulting from this metabolism. Genetic polymorphisms in CYP enzymes have been proposed as a biomarker of susceptibility to environmental toxicants (Hong and Yang, 1997). Furthermore, co-exposure with other agents such as ethanol may increase susceptibility to carbon tetrachloride. While it is difficult to quantify the range of susceptibility, as indicated earlier in this report, human subjects have exhibited a wide range of response severity.

Species variability in the metabolism and disposition of carbon tetrachloride has been addressed in several PBPK models and application of the models. The PBPK model of Paustenbach et al. (1988) predicted fat and venous blood concentrations of carbon tetrachloride to be notably higher in rats than in humans at exposure concentrations of 5 ppm. Gargas et al. (1989) reported higher blood:air partition coefficients for rats than for humans. The greater respiratory rates, greater cardiac output/tissue perfusion rates in rodents in conjunction with the higher blood:air partition coefficients argues for a greater tissue dose in rodents than in humans at equivalents exposure concentrations. Based upon PBPK model predictions, Delic et al. (2000) showed that the ratio of rate and extent of metabolism in rats was greater than that for humans at low concnetrations (5 ppm NOAEL for rats and United Kingdom occupational exposure limit of 2 ppm).

4.4.2 Concurrent Exposure Issues

The potentiation of carbon tetrachloride hepatotoxicity by ethanol, aliphatic alcohols, and ketones has been well documented in animals and humans (Folland et al., 1976; reviewed in ATSDR, 2003; see also Section 2.2.1). Folland et al. (1976) reported on an individual who exhibited only a modest, transient

increase in serum transaminase activity, but experienced renal failure following acute inhalation of carbon terachloride. This individual was thought to have been preexposed to isopropanol, which induces CYP2E1 and thereby markedly potentiates acute $CC1_4$ cytotoxicity. Potentiation of carbon tetrachloride-induced toxicity in humans by ethanol has also been documented (Markham, 1967; Manno and Rezzadore, 1994; Manno et al., 1996). Although the precise mechanism of potentiation has not been elucidated for all interactions, the enhancement of metabolic processes resulting in increased production of reactive metabolites has been demonstrated. Because the toxicity of carbon tetrachloride is mediated by CYP2E1, it may be assumed that modulation of CYP2E1 expression by other chemicals (see review by Raucy, 1995) may alter the impact of carbon tetrachloride-initiated toxicity. In a recent report by Wang et al. (1995), it was shown that prior exposure of rats to ethanol (2 g/day) for three weeks resulted in a 2-fold increase in the hepatotoxicity of (as determined by serum enzyme activities) carbon tetrachloride following a 6-hour inhalation exposure to 50 ppm and a 20 to 30-fold increase following a 6-hour exposure to 500 ppm.

Cornish et al. (1967) reported on the effects of aliphatic alcohol pretreatment on the toxicity of carbon tetrachloride exposure (1,000 ppm for 2 or 2.5 hours) in male albino rats. Based upon SGOT activity, the 1,000 ppm carbon tetrachloride exposures had little effect on SGOT activity relative to unexposed controls (246 ± 20 vs 238 ± 8 units) but most of the alcohols studied resulted in notable increases in SGOT activity in combination with carbon tetrachloride relative to carbon tetrachloride alone ($1{,}941 \pm 558$ vs 217 ± 17 units).

A remarkable potentiation of carbon tetrachloride-induced lethality prior to exposures to non-toxic levels of chlordecone has been documented in animal models (Mehendale, 1994). Although such synergistic responses are often the result of altered metabolism, the chlordecone-potentiated carbon tetrachloride lethality appears to be the result of alteration of tissue repair processes resulting in an amplification of the toxic insult rather than altered biotransformation (Mehendale, 1990).

5. DATA ANALYSIS FOR AEGL-1

5.1 Summary of Human Data Relevant to AEGL-1

Tomenson at al. (1995) affirmed that occupational exposure to carbon tetrachloride at mean exposures up to 4 ppm resulted in only minor alterations of serum enzyme activity. Based upon estimated exposure concentrations and the responses of four individuals under controlled conditions, Davis et al. (1934) reported that exposures of 158 ppm for 30, and 76 ppm for either two and one-half hours or four hours were without signs or symptoms of toxicity. Six subjects exposed to a TWA of 49 ppm for 70 minutes noted only odor detection and no irritation or symptoms of toxicity. Minor transient changes in serum iron, serum transaminases, and urinary urobilinogen were detected in two subjects exposed for 70 minutes (Stewart et al., 1961). In the same study six subjects were exposed to a TWA of 10.9 ppm for 180 minutes; no adverse effects were detected. In a report of an occupational exposure study, Smyth et al. (1936) concluded that exposure to 5-117 ppm (8-hr TWA) resulted in minimal effects (restricted visual field and slightly elevated bilirubin). However, Elkins (1942) noted that exposures to 20-85 ppm produced notable signs of toxicity (nausea, vomiting, weight loss).

5.2 Summary of Animal Data Relevant to AEGL-1

Animal data defining no effect or minimal effects that are consistent with the derivation of AEGL-1 values are limited and equivocal. Smyth et al. (1936) found no significant signs of toxicity in rats exposed to 200 ppm carbon tetrachloride, 8 hrs/day, 5 days/week for 10.5 months while Appelman et

al. (1985) using a similar exposure protocol (6 hrs/day, 5 days/week) reported transient hepatic effects and elevated serum enzyme activities in rats at four weeks of exposure to only 63 ppm. Although Adams et al. (1952) reported no adverse effects in rats exposed to 3,000 ppm (6 min), 800 ppm (30 min), and 50 ppm (420 min), serum enzyme activities were not measured and, therefore, it is possible that hepatotoxic effects may have been overlooked. Paustenbach et al. (1986b) reported no significant changes in SDH activity in rats exposed to 100 ppm for eight hours. David et al. (1981) noted minor changes in SGPT activity and minor histopathologic findings in rats exposed to 1,000 ppm for 18 minutes, 250 ppm for 72 minutes, 50 ppm for 6 hours, or following six 3-minutes exposures (at 1-hr intervals) to 1,000 ppm. Minor increases in activities of some serum enzymes were reported by Cornish and Block (1960) for rats exposed to 250, 1000 or 1500 ppm for four hours but not for rats exposed to 50 or 100 ppm for four hours. Although several lethality studies (Union Carbide, 1947; Adams et al., 1952; Dow Chemical, 1986) provided data showing no lethalities, these investigations were not assessing other toxicity endpoints and, therefore, it can not be assumed that the animals surviving the exposures were devoid of toxic effects above and beyond what would be considered for AEGL-1 assessments.

5.3 Derivation of AEGL-1

Although not a robust data set, the human experience data are considered appropriate for derivation of AEGL-1 values and eliminate the uncertainties inherent in extrapolating from animal data. Furthermore, the limited animal data regarding effects consistent with AEGL-1 are equivocal. Data reported by Tomenson at al. (1995) affirmed that occupational exposure to carbon tetrachloride at mean exposures up to 4 ppm resulted in only minor alterations of serum enzyme activity. However, the findings were based upon an exposure duration (long-term, repeated exposure) that was inappropriate for derivation of AEGL values. Reports by Davis et al. (1934) and Stewart et al. (1961) both provided human exposure data that are appropriate for derivation of an AEGL-1. Both were controlled exposure studies using human volunteers exposed to low levels of carbon tetrachloride for durations consistent with AEGL concerns.

The results of the Davis (1934) study showed only minimal effects in four human subjects exposed to 158 ppm carbon tetrachloride for 30 minutes; one of the four subjects experienced a feeling of nervousness while the remaining three subjects experienced no effects. Additionally, no CNS or renal effects resulted from exposure of the human volunteers to 76 ppm for four hours. The 4-hour exposure to 76 ppm was used as the point-of-departure for deriving the AEGL-1 values. Temporal extrapolation to the AEGL-specific time points from the 4-hour exposure data were based on the exponential function $C^n \times t = k$, where n = 2.5 based on lethality data in rats (see Section 7.3). An uncertainty factor of 3 for protection of sensitive individuals was applied to account for variability in possible CNS effects. Because CNS effects are independent of metabolism, and because the CNS response to volatile organic solvents has been shown to exhibit limited variability among individuals and among age groups (Gregory et al., 1969; de Jong et al., 1975; Stevens et al., 1975), the uncertainty adjustment for individual variability was limited to 3. The AEGL-1 values are shown in Table 12 and their derivations presented in Appendix A. The data used to develop the AEGL-1 values are supported by occurrence of only minimal effect in one of the four individuals exposed for 30 minutes to 158 ppm.

TABLE 12. AEGL-1 FOR CARBON TETRACHLORIDE (ppm [mg/m^3])

AEGL Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	58 [365]	58 [365]	44 [277]	25 [157]	19 [120]

6. DATA ANALYSIS FOR AEGL-2

6.1 Summary of Human Data Relevant to AEGL-2

Several reports provided data describing nonlethal effects of acute exposure of humans to carbon tetrachloride. Davis et al. (1934) conducted experiments in which three human subjects were exposed to 317 ppm carbon tetrachloride (concentration calculated based upon room volume and amount of carbon tetrachloride) for 30 minutes. Nausea, vomiting, and headaches were reported by the subjects but clinical assessments (urinalysis, blood count, hemoglobin levels, blood pressure and heart rate) remained normal for up to 48 hours postexposure. Similar effects were reported by subjects exposed to 1,191 ppm for 15 minutes with the exception that one of the four subjects found the exposure to be intolerable after 9 minutes. Exposures of 12,800 ppm for 3-7 minutes produced these effects in addition to dizziness and signs of anesthesia. The observed effects were apparently not long-lasting but may be considered severe enough to impair escape or normal function and, therefore, can be considered as a conservative endpoint for deriving AEGL-2 values. Davis et al. (1934) also reported notable renal effects in a worker experimentally exposed to 200 ppm for 8 hours. At two month postexposure, renal function had returned to near normal.

6.2 Summary of Animal Data Relevant to AEGL-2

Animal data were limited to descriptions of effects indicative of hepatotoxicity following highly varied exposure regimens (Adams et al., 1952; David et al., 1981; Appleman et al., 1985; Belyaev et al., 1992) and one report (Sakata et al., 1987) that noted a "comatose" condition in rats following a 15-minute exposure to 180 ppm. Adams et al. (1952) characterized the severity of response of rats to various inhalation exposure protocols. Because the determination of adverse or not adverse was based upon responses characteristic of notable hepatic insult (e.g., liver weight change, increased lipid content, gross and microscopic changes), the adverse effects are considered to be consistent with AEGL-2 effects. Adverse effects were detected following exposures to 12,000 ppm for three minutes, 3,000 ppm for nine minutes, 800 ppm for 60 minutes, and 400 ppm for 420 minutes. Minor changes in SGPT activity were reported by David et al. (1981) for rats exposed to 300 ppm·hr under different exposure regimens; 1,000 ppm for 18 minutes, 250 ppm for 72 minutes, 50 ppm for 6 hours, or six 3-minute exposures to 1,000 ppm at 1-hour intervals. Four-week exposure of rats to 63 or 80 ppm, 6 hrs/day, 5 days/week resulted in transient hepatic effects and 2 to 9-fold increases in serum enzyme levels. However, no data were provided relative to acute exposures. Mice exposed to 4,770 ppm carbon tetrachloride for 4 hours exhibited centrilobular necrosis in the liver (Belyaev et al., 1992). With the exception of the centrilobular necrosis reported by Belyaev et al. (1992), and the "comatose" effects reported by Sakata et al. (1987), and the hepatic damage noted by Adams et al. (1952), the available animal data do not suggest a severity that is consistent with AEGL-2 effects. Furthermore, the liver is primarily affected by $CC1_4$ in rodents, whereas hepatic injury is often relatively minor in $CC1_4$-poisoned humans where kidney damage predominates.

6.3 Derivation of AEGL-2

The AEGL-2 values were derived using human exposure data. Although the human data are limited, their use precludes the uncertainty inherent in extrapolating from animal data. Additionally, animal data consistent with AEGL-2 effects were also quite limited.

The AEGL-2 was derived based upon exposure to 1,191 ppm carbon tetrachloride wherein one of four human subjects found a 9-minute exposure to be intolerable (Davis, 1934); other subjects tolerated

the exposure up to 15 minutes. The effects reported by these subjects included headache, and nausea and vomiting. Extrapolation from the 9-minute exposure period to other AEGL-specific periods was based on the exponential function $C^n \times t = k$, where n was determined to be 2.5 as determined from lethality data in rats (see Section 7.3). Similar to the development of AEGL-1 values, the adjustment for uncertainty regarding individual variability was limited to 3 because CNS-mediated effects are not metabolism-mediated and exhibit limited variability among individuals. The AEGL-2 values are shown in Table 13 and their derivations presented in Appendix A.

TABLE 13. AEGL-2 FOR CARBON TETRACHLORIDE (ppm [mg/m^3])

AEGL Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	380 [2390]	250 [1573]	190 [1195]	100 [629]	81 [509]

7. DATA ANALYSIS FOR AEGL-3

7.1 Summary of Human Data Relevant to AEGL-3

Although data for human lethality following acute exposures to carbon tetrachloride are available, concentration and/or duration terms are lacking. Norwood et al. (1950) provided the only quantitative exposure data regarding a human fatality in a heavy drinker following acute exposure to carbon tetrachloride. The exposure time (15 minutes) was an approximate value and the concentration (250 ppm) was determined based upon a reconstruction of the accident using room volume and the amount of carbon tetrachloride dispersed.

7.2 Summary of Animal Data Relevant to AEGL-3

Lethality data are available for squirrel monkeys, dogs, rats, mice, and guinea pigs. The squirrel monkey and guinea pig data are not acute exposures, and the dog data is compromised the use of only one animal. The most complete data sets are those provided by Adams et al. (1952), Union Carbide (1947), and Dow Chemical (1986) for rats exposed to carbon tetrachloride at concentrations ranging from 1,000 to 20,000 ppm for durations ranging from 0.1 to 10 hours (these exposure periods were not for all concentrations).

7.3 Derivation of AEGL-3

The case report of Norwood et al. (1950) provides evidence of alcohol-potentiated lethal toxicity of carbon tetrachloride. The exposure terms were based on a reconstruction of the accident. Although not used for the derivation of AEGL-3 values, this information is useful for comparative purposes and to demonstrate individual variability in the toxic response to inhaled carbon tetrachloride.

Rat lethality data from the Adams et al. (1952) and Dow Chemical (1986) reports were used to derive AEGL-3 values. The method of Litchfield and Wilcoxon (1949) was used to obtain an estimate of a lethality threshold (LC_{01}) using 1-hour lethality data. Other than 1-hour exposures were scaled to 1-hour duration using $C^n \times t = k$ where n = 2.5. The exponent, n = 2.5 was determined empirically from rat lethality data (Appendix C). With the exception of a 5-hr exposure at 4,600 ppm (Adams et al., 1952), scaling was applied to exposure periods of 0.5 to 2.2 hours used in the study by Adams et al. The resulting 1-hr LC_{01} of 5,153.5 ppm (Appendix B) was used as the basis for scaling to other AEGL-specific time periods. Due to the known variabilities in the metabolic disposition of carbon tetrachloride that may result in an altered toxic response (e.g., alcohol-induced potentiation of renal and hepatotoxicity), an uncertainty factor of 10 was retained for protection of susceptible individuals. For application of an uncertainty factor for interspecies variability, several data elements were considered. It has been noted that rats eliminate CCl_4 faster than larger species (Andersen, 1981; Reitz et al., 1982) such as monkeys (McCollister et al., 1951) and humans (Stewart et al., 1961) and that rat studies may underestimate the accumulation of CCl_4 in tissues of humans. PBPK model results, however, predict that rodents will attain higher levels of carbon tetrachloride in venous blood and fat than would humans similarly exposed (Paustenbach et al., 1988). Additionally, Delic et al. (2000) utilized PBPK model predictions to emphasize the greater metabolism of carbon tetrachloride by rats relative to humans. Overall, PBPK models affirm notably greater sensitivity of rodent species to carbon tetrachloride toxicity based upon metabolism and disposition considerations. Therefore, an interspecies uncertainty factor was not applied. Additional data considerations also support this approach. In subchronic inhalation studies using rats, Smyth et al. (1936) showed that long-term exposures (8 hrs/day, 5 days/week for 10 ½ months) to concentrations as high as 400 ppm did not result in lethality. Similarly, daily (7 hrs/day) exposure of a mongrel dog for six months to 400 ppm resulted only in body weight loss (Union Carbide, 1947). The long-term exposure data for animals appear to support minimization of an interspecies uncertainty factor.

Regression analysis of concentration-time relationships for rat lethality data (Union Carbide, 1947; Adams et al., 1952; Dow Chemical, 1986) using the method of ten Berge et al. (1986), revealed that n = 2.5 (Appendix 3). This is slightly lower than the n of 2.8 reported by ten Berge (1986). The current analysis, however, utilized two additional data sets in addition to that of Adams et al. (1952) used by ten Berge. The resulting AEGL-3 values are shown in Table 14 and their derivations are presented in Appendix A.

TABLE 14. AEGL-3 FOR CARBON TETRACHLORIDE (ppm [mg/m^3])					
AEGL Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	1100 [6920]	680 [4227]	520 [3270]	300 [1887]	220 [1384]

8. SUMMARY OF AEGL VALUES

8.1 AEGL Values and Toxicity Endpoints

A relational comparison of the AEGL values is shown in Table 15. The AEGL-1 was based upon human data indicating no serious toxic effect during controlled acute inhalation exposures. The AEGL-2 values were also based upon human exposure data from controlled acute inhalation exposures in which the subjects experienced notable signs and symptoms of toxicity (nausea, vomiting, headache, intolerance to the exposure). Although limited clinical chemistry data suggested no definitive systemic toxic effects, the reported signs and symptoms were such that normal function and ability to escape may be impaired. The AEGL-3 values were based upon an estimate of the lethality threshold in rats. Data from nonhuman primates indicated that chronic exposures to concentrations greater than the 8-hr AEGL-3 value were not lethal.

TABLE 15. RELATIONAL COMPARISON OF AEGL VALUES FOR CARBON TETRACHLORIDE (ppm [mg/m^3])					
Classification	10-min	30-min	1-hour	4-hour	8-hour
AEGL-1	58 [365]	58 [365]	44 [277]	25 [157]	19 [120]
AEGL-2	380 [2390]	250 [1573]	190 [1195]	100 [629]	81 [509]
AEGL-3	1100 [6920]	680 [4227]	520 [3270]	300 [1887]	220 [1384]

Although a carcinogenic response has been observed for animals following oral exposure to carbon tetrachloride, quantitative data regarding a carcinogenic response following inhalation exposure to carbon tetrachloride were not available. Therefore, the AEGLs have been based on noncarcinogenic endpoints. Route-to-route extrapolation from oral exposure data was not performed due to the great uncertainties involved.

8.2 Extant Standards and Guidelines for Carbon Tetrachloride

Available exposure standards and guidelines for carbon tetrachloride have been established by several organizations (Table 16).

TABLE 16. Extant Standards and Guidelines for Carbon Tetrachloride

Guideline	Exposure Duration					
		10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-1		58 ppm	58 ppm	44 ppm	25ppm	19 ppm
AEGL-2		380 ppm	250 ppm	190 ppm	100 ppm	81 ppm
AEGL-3		1100 ppm	680 ppm	520 ppm	300 ppm	220 ppm
ERPG-1[a]				20 ppm		
ERPG-2				100 ppm		
ERPG-3				750 ppm		
NIOSH REL[b]				2 ppm		
NIOSH IDLH[c]			200 ppm			
MAK[d]			0.5			
MAC[e]						2 ppm
OSHA PEL TWA[f]	10 ppm					
ACGIH TLV-TWA[g] ACGIH STEL[h]						5 ppm 10 ppm

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2001)
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b]**NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit)** (NIOSH 2001) is defined analogous to the ACGIH TLV-TWA.

[c]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 2001) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[d]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] 2000) is defined analogous to the ACGIH-TLV-TWA.

[e]**MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands) (National MAC List 1999) is defined analogous to the ACGIH-TLV-TWA.

[f]**OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 1989) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[g]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2001) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[h]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 2001) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

8.3 Data Quality and Research Needs

The overall database for carbon tetrachloride was sufficient for developing all tiers of AEGL values. Both human and animal data were available for review and analysis. Human data were used as the basis for the AEGL-1 and AEGL-2 values, thereby avoiding the uncertainties inherent to animal-to-human extrapolations. Metabolism data for carbon tetrachloride and the consequent ramifications of metabolism on the toxic response to carbon tetrachloride allowed for the characterization/identification of an important sensitive population (those with enhanced cytochrome oxidase activity) and relevant adjustments in the AEGL values to account for this group. Although the AEGL-2 endpoint is not indicative of a serious toxicologic effect, it represents responses that would compromise normal function and escape from a hazardous situation. AEGL-3 values were based upon animal lethality data sufficient to estimate a lethality threshold in the test animals, and were developed with considerations regarding metabolism and disposition data suggesting greater sensitivity of rodent test species.

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APPENDIX A
DERIVATION OF AEGL VALUES

DERIVATION OF AEGL-1 VALUES

Key study: Davis, 1934

Toxicity endpoint: humans; no CNS effects in volunteer subjects exposed to 76 ppm for 4 hours

Scaling: $C^{2.5} \times t = k$ (ten Berge, 1986) (see Appendix C)
$(76 \text{ ppm})^{2.5} \times 4 \text{ hrs} = 201{,}416.0 \text{ ppm}^{2.5}\cdot\text{hr}$

Uncertainty factors: 3 for protection of sensitive individuals; metabolism will be irrelevant for CNS effects

10-min AEGL-1

10-min value equivalent to 30 minute value (58 ppm) due to uncertainty in extrapolating from a 4-hour experimental exposure duration

30-min AEGL-1

$$C^{2.5} \times 0.5 \text{ hr} = 201{,}416.0 \text{ ppm}^{2.5}\cdot\text{hr}$$
$$C = 174.6 \text{ ppm}$$
30-min AEGL-1 = 174.6 ppm/3 = 58.2 ppm (366 mg/m^3) rounded to 58 ppm (366 mg/m^3)

1-hr AEGL-1

$$C^{2.5} \times 1 \text{ hr} = 201{,}416.0 \text{ ppm}^{2.5}\cdot\text{hr}$$
$$C = 1323 \text{ ppm}$$
1-hr AEGL-1 = 132.3 ppm/3 = 44.1 ppm (277 mg/m^3) rounded to 44 ppm (277 mg/m^3)

4-hr AEGL-1

$$C^{2.5} \times 4 \text{ hrs} = 201{,}416.0 \text{ ppm}^{2.5}\cdot\text{hr}$$
$$C = 76 \text{ ppm}$$
4-hr AEGL-1 = 76 ppm/3 = 25.3 ppm (159 mg/m^3) rounded to 25 ppm (159 mg/m^3)

8-hr AEGL-1

$$C^{2.5} \times 8 \text{ hrs} = 201{,}416.0 \text{ ppm}^{2.5}\cdot\text{hr}$$
$$C = 57.6 \text{ ppm}$$
8-hr AEGL-1 = 57.6 ppm/3 = 19.2 ppm (120.8 mg/m^3) rounded to 19 ppm (120 mg/m^3)

AEGL-2

Key study: Davis et al., 1934

Toxicity endpoint: humans; nausea, vomiting, headache, intolerance in one subject following 9-minute exposure to 1,191 ppm

Scaling: $C^{2.5} \times t = k$ (ten Berge, 1986) (see Appendix C)
$(1{,}191 \text{ ppm})^{2.5} \times 0.15 \text{ hrs} = 7{,}342{,}951.55 \text{ ppm·hr}$

Uncertainty factors: 3 for protection of sensitive individuals; CNS effects are not metabolism mediated and unlikely to vary substantially among individuals

10-min AEGL-2

$C^{2.5} \times 0.167 \text{ hr} = 7{,}342{,}951.55 \text{ ppm·hr}$
$C = 1{,}140.94 \text{ ppm}$
10-min AEGL-2 = 1140.94 ppm/3 = 380.3 ppm rounded to 380 ppm (2390 mg/m^3)

30-min AEGL-2

$C^{2.5} \times 0.5 \text{ hr} = 7{,}342{,}951.55 \text{ ppm·hr}$
$C = 735.8 \text{ ppm}$
30-min AEGL-2 = 735.8 ppm/3 = 245.3 ppm rounded to 250 ppm (1573 mg/m^3)

1-hr AEGL-2

$C^{2.5} \times 1 \text{ hr} = = 7{,}342{,}951.55 \text{ ppm·hr}$
$C = 557.63 \text{ ppm}$
1-hr AEGL-2 = 557.63 ppm/ 3 =-185.9 ppm rounded to 190 ppm (1195 mg/m^3)

4-hr AEGL-2

$C^{2.5} \times 4 \text{ hrs} = 7{,}342{,}951.55 \text{ ppm·hr}$
$C = 320.28 \text{ ppm}$
4-hr AEGL-2 = 320.28 ppm/3 = 106.8 ppm rounded to 100 ppm (629 mg/m^3)

8-hr AEGL-2

$C^{2.5} \times 8 \text{ hrs} = 7{,}342{,}951.55 \text{ ppm·hr}$
$C = 242.72 \text{ ppm}$
8-hr AEGL-2 = 242.72 ppm/3 = 80.9 ppm rounded to 81 ppm (509 mg/m^3)

AEGL-3

Key study: Union Carbide 1946; Adams et al., 1952; Dow Chemical 1986

Toxicity endpoint: Rats; lethality; estimate of LC_{01} (5,153.5 ppm) based upon 1-hr exposure (see Appendix C)

Scaling: $C^{2.5} \times t = k$ (ten Berge, 1986)
$(5153.5 \text{ ppm})^{2.5} \times 1 \text{ hr} = 1{,}906{,}582{,}933 \text{ ppm·hr}$

Uncertainty factors: 10 for protection of sensitive individuals (e.g.,ethanol-induced P-450)
1 for interspecies variability; results of PBPK models clearly indicate that the kinetics of carbon tetrachloride are markedly different in rodents than in humans, resulting in rodents exhibiting greater sensitivity in toxic responses.

10-min AEGL-3

$C^{2.5} \times 0.167 \text{ hr} = 1{,}906{,}582{,}933 \text{ ppm·hr}$
$C = 10{,}544 \text{ ppm}$
10-min AEGL-3 = 10,544 ppm/ 10 = 1054 ppm rounded to 1100 ppm (6920 mg/m^3)

30-min AEGL-3

$C^{2.5} \times 0.5 \text{ hr} = 1{,}906{,}582{,}933 \text{ ppm·hr}$
$C = 6{,}800 \text{ ppm}$
30-min AEGL-3 = 6,800 ppm/10 = 680 ppm (4277 mg/m^3)

1-hr AEGL-3

$C^{2.5} \times 1 \text{ hr} = 1{,}906{,}582{,}933 \text{ ppm·hr}$
$C = 5{,}153.5 \text{ ppm}$
1-hr AEGL-3 = 5,153.5 ppm/10 = 515.4 ppm rounded to 520 ppm (3270 mg/m^3)

4-hr AEGL-3

$C^{2.5} \times 4 \text{ hrs} = 1{,}906{,}582{,}933 \text{ ppm·hr}$
$C = 2959.9 \text{ ppm}$
4-hr AEGL-3 = 2,959.9 ppm/10 = 295.9 ppm rounded to 300 ppm (1887 mg/m^3)

8-hr AEGL-3

$C^{2.5} \times 8 \text{ hrs} = 1{,}906{,}582{,}933 \text{ ppm·hr}$
$C = 2{,}243 \text{ ppm}$
8-hr AEGL-3 = 2,243 ppm/10 = 224.3 ppm rounded to 220 ppm (1384 mg/m^3)

APPENDIX B
DERIVATION OF EXPONENTIAL FUNCTION FOR TEMPORAL SCALING AND DERIVATION OF LETHALITY THRESHOLD VALUE

Concentration-Time Mortality Response Relationship for Rats

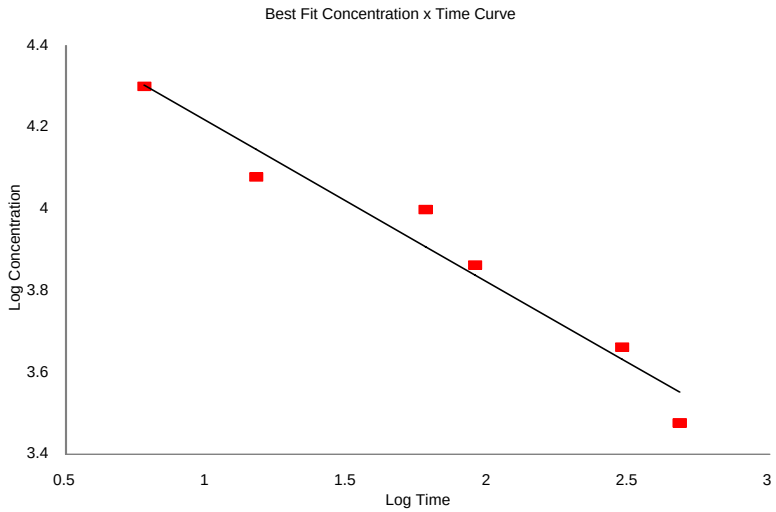
Data sources: Adams et al., 1952; Dow Chemical, 1986

Time	Conc.	Log Time	Log Conc.
6	20000	0.7782	4.3010
15	12000	1.1761	4.0792
60	10000	1.7782	4.0000
90	7300	1.9542	3.8633
300	4600	2.4771	3.6628
480	3000	2.6812	3.4771

Regression Output:

Intercept	4.6106	
Slope		-0.3947
R Squared		0.9545
Correlation		-0.9770
Degrees of Freedom		4
Observations		6

n = 2.53
k = 4.813E+11



Estimation of Lethal Response by Rats to Carbon Tetrachloride

Data Sources: Adams et al., 1952; Dow Chemical, 1986.

Dose	Mortality	Observed%	Expected%	Observed-Expected	Chi-Square
7300.000	0/20	0(7.20)	4.43	2.77	0.0181
8750.000	0/20	0(8.60)	9.30	-0.70	0.0006
10000.000	0/5	0(9.40)	15.54	-6.14	0.0287
11760.000	0/5	0(10.30)	27.23	-16.93	0.1446
12000.000	3/10	30.00	29.02	0.98	0.0005
13200.000	5/10	50.00	38.29	11.71	0.0580
15150.000	8/10	80.00	53.14	26.86	0.2897
15800.000	7/10	70.00	57.68	12.32	0.0621
19000.000	9/19	47.37	75.35	-27.98	0.4215
26000.000	20/20	100(93.80)	92.35	1.45	0.0030

Values in parentheses are corrected for 0 or 100 percent Total = 1.0268

LD50 = 14720.510(12841.527 - 16874.428)*
Slope = 1.46(1.26 - 1.69)*
* These values are 95 percent confidence limits

Total animals = 129 Total doses = 10 Animals/dose = 12.90
Chi-square = total chi-square X animals/dose = 13.2454
Table value for Chi-square with 8 Degrees of Freedom = 15.5100

Expected Lethal Dose Values

LD0.1	3039.445
LD1.0	5153.488
LD5.0	7513.524
LD10	8911.792
LD25	11453.651
LD50	14720.510
LD75	18919.156
LD90	24315.358
LD99	42047.909

APPENDIX C
CARCINOGENICITY ASSESSMENT FOR CARBON TETRACHLORIDE

CANCER ASSESSMENT OF CARBON TETRACHLORIDE

An inhalation unit risk of 1.5E-5 $\mu g/m^3$ was derived by the U.S. EPA (U.S. EPA, 1992) by route-to-route extrapolation from animal data sets. A carbon tetrachloride concentration of 7E-2 $\mu g/m^3$ would be associated with a risk level of 1 in 100,000.

To convert a 70-year exposure to a 24-hour exposure:

24-hr exposure = d x 25,600; where d = 7×10^{-2} $\mu g/m^3$
= (7×10^{-2} mg/m^3) x 25,600 days
= 1,792 $\mu g/m^3$ (1.79 mg/m^3)

To account for uncertainty regarding the variability in the stage of the cancer process at which carbon tetrachloride or its metabolites may act, a multistage factor of 2.8 is applied (Crump and Howe, 1984):

(1.79 mg/m^3)/2.8 = 0.64 mg/m^3

For a 1×10^{-4} risk, the extent of risk based on the 24-hr exposure concentration becomes:

$$0.64\ mg/m^3 \times \frac{1 \times 10^{-4}}{1 \times 10^{-6}\ (\text{risk at d})} = 64\ \mu g/m^3 \text{ or } 0.18\ mg/m^3$$

Therefore, based upon the potential carcinogenicity of carbon tetrachloride, an acceptable 24-hr exposure would be 64 mg/m^3 (10.2 ppm).

If the exposure is limited to a fraction (f) of a 24-hr period, the fractional exposure becomes 1/f x 24 hrs (NRC, 1985). For a 10^{-4} risk:

24-hr exposure	=	64 mg/m^3 (10.2 ppm)
8-hr	=	192 mg/m^3 (31 ppm)
4-hr	=	384 mg/m^3 (61 ppm)
1-hr	=	1,536 mg/m^3 (244 ppm)
0.5 hr	=	3,072 mg/m^3 (488 ppm)

No data are available regarding the potential carcinogenicity of carbon tetrachloride following inhalation exposure. The cancer risk discussed here is based upon route-to-route extrapolation from oral exposure data which has inherent uncertainty. For these reasons, the AEGL values were based upon noncarcinogenic toxicity endpoints resulting from acute inhalation exposures.

APPENDIX D
SUMMARY TABLES FOR CARBON TETRACHLORIDE AEGL VALUES

ACUTE EXPOSURE GUIDELINES FOR CARBON TETRACHLORIDE (CAS NO. 56-23-5)

AEGL-1 VALUES

10 minutes	30 minutes	1 hour	4 hours	8 hours
58 ppm	58 ppm	44 ppm	25 ppm	19 ppm

Reference: Davis, P.A. 1934. Carbon tetrachloride as an industrial hazard. JAMA 103: 962-966.

Test Species/Strain/Number: human volunteers, four subjects (gender not specified) 20-30 years of age

Exposure Route/Concentrations/Durations: inhalation, 76 ppm for 4 hours

Toxicity Endpoint: absence of CNS and renal effects

Time Scaling: $C^n \times t = k$, where n = 2.5; based on regression analysis of rat lethality data of Adams et al., (1952)

Concentration/Time Selection/Rationale: 4-hour exposure to 76 ppm produced no CNS or renal effects

Uncertainty Factors/Rationale

Total Uncertainty Factor: 3

Interspecies: none; human subjects

Intraspecies: 3; to account for variability in disposition and response of sensitive individuals. CNS effects will be independent of metabolism

Modifying Factor: none

Animal-to-Human Dosimetric Adjustments: none; human subjects

Data Adequacy: The AEGL-1 values are supported by additional data from Davis (1934) showing that human subjects were asymptomatic following a 30-minute exposure to 158 ppm.

ACUTE EXPOSURE GUIDELINES FOR CARBON TETRACHLORIDE (CAS NO. 56-23-5)

AEGL-2 VALUES

10 minutes	30 minutes	1 hour	4 hours	8 hours
380 ppm	250 ppm	190 ppm	100 ppm	81 ppm

Reference: Davis, P.A. 1934. Carbon tetrachloride as an industrial hazard. JAMA 103: 962-966.

Test Species/Strain/Number: four human subjects (gender not specified), 19-40 years of age

Exposure Route/Concentrations/Durations: inhalation; 1,191 ppm for 15 minutes

Toxicity Endpoint: headache, nausea, vomiting, and intolerance to exposure

Time Scaling: $C^n \times t = k$, where n = 2.5; based on regression analysis of lethality data from Adams et al. (1952)

Concentration/Time Selection/Rationale: 9-minute exposure to 1,191 ppm CCl_4 resulted in headache, nausea, and vomiting, which may impair escape. However, clinical assessments (urinalysis, blood count, hemoglobin levels, blood pressure and heart rate) were normal at 48 hours postexposure.

Uncertainty Factors/Rationale:
Total Uncertainty Factor: 3
Interspecies: none; human subjects
Intraspecies: 3; to account for individual variability in disposition of CCl_4 resulting in variability in the sensitivity to carbon tetrachloride-induced CNS-mediated effects. CNS effects are not metabolism mediated and unlikely to vary substantially among individuals.

Modifying Factor: none

Animal-to-Human Dosimetric Adjustments: none; human subjects

Data Adequacy: Although not indicative of irreversible effects, the critical effects used as the basis for the AEGL-2 values may result in a compromised ability to egress from the exposure situation thereby creating a potential for more serious effects consistent with AEGL-2 definition. Dermal absorption potential is not addressed by the AEGL values.

ACUTE EXPOSURE GUIDELINES FOR CARBON TETRACHLORIDE (CAS NO. 56-23-5)

AEGL-3 VALUES

10 minutes	30 minutes	1 hour	4 hours	8 hours
1100 ppm	680 ppm	520 ppm	300 ppm	220 ppm

References: Adams, E.M., Spencer, H.C., Rowe, V.K., McCollister, D.D., Irish, D.D. 1952. Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Arch. Ind. Hyg. Occup. Med. 6: 50-66.
Dow Chemical. 1986. Comparison of the result of exposure of rats and cavies to the vapors of carbon tetrachloride and bromochloromethane. Dated 7/11/60. EPA-OTS 86-870002363.

Test Species/Strain/Number: Rats/albino or not specified/5-30 per group

Exposure Route/Concentrations/Durations: inhalation/3,000-20,000 ppm/0.1-12 hrs

Toxicity Endpoint: lethality (estimated 1-hr LC_{01} of 5,135.5 ppm in rats)

Time Scaling: $C^n \times t = k$, where n = 2.5; based on regression analysis of lethality data from Adams et al. (1952)

Concentration/Time Selection/Rationale: estimated 1-hr LC_{01} (5,153.5 ppm, 1 hr)

Uncertainty Factors/Rationale:
Total Uncertainty Factor: 10
Interspecies: 1 results of PBPK models clearly indicate that the kinetics of carbon tetrachloride are markedly different in rodents than in humans, resulting in rodents exhibiting greater sensitivity in toxic responses. Smyth et al. (1936) showed that exposure (6 hrs/day, 5 days/week for 10.5 months) of monkeys to 200 ppm caused only slight liver damage; the 8-hr AEGL-3 of 75 ppm is well below a level tolerated by a nonhuman primate following chronic exposure
Intraspecies: 10 to account for individual variability in the sensitivity to carbon tetrachloride-induced toxicity (e.g., alcohol-potentiated hepatotoxicity)

Modifying Factor: none

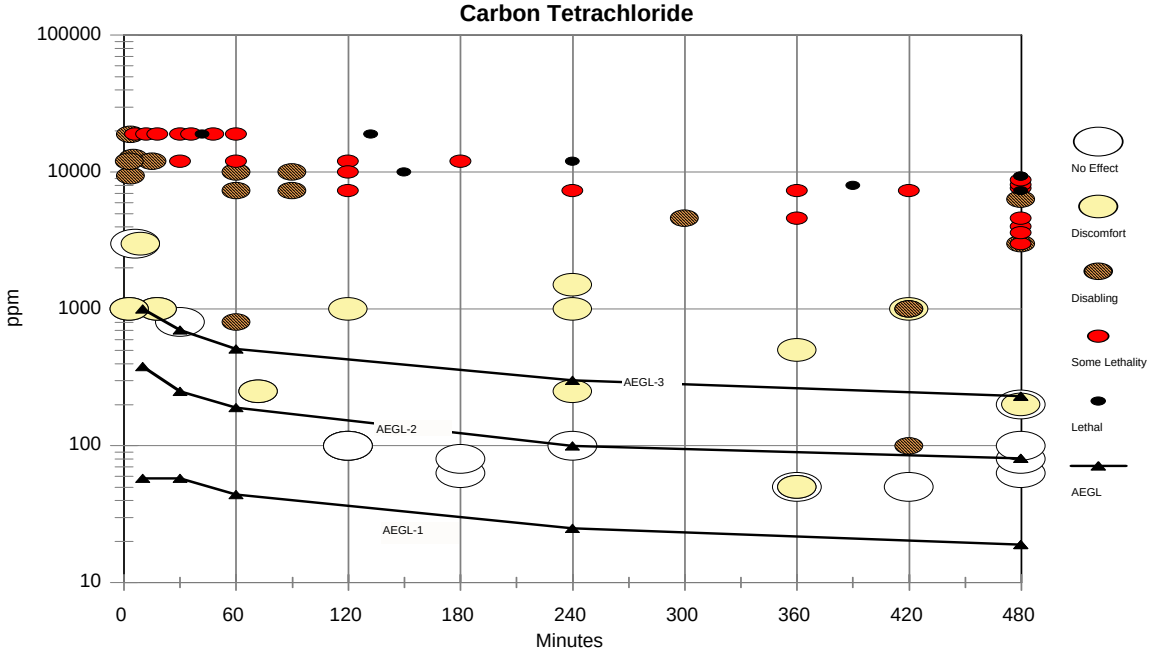
Animal-to-Human Dosimetric Adjustments: insufficient data

Data Adequacy: The AEGL-3 values are supported by subchronic exposure studies in animals showing that exposures above the AEGL-3 values did not result in lethality. Dermal absorption

potential is not addressed by the AEGL values.

APPENDIX E
CATEGORY PLOTS FOR CARBON TETRACHLORIDE

Chemical Toxicity - TSD Animal Data
Carbon Tetrachloride



Chemical Toxicity - TSD Human Data
Carbon Tetrachloride